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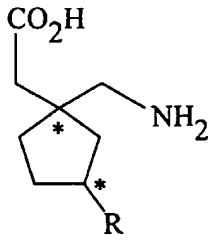
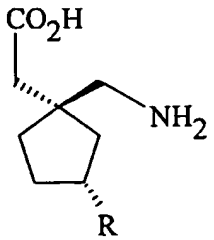
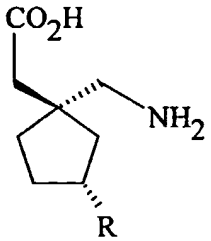
(54) Title: METHOD FOR THE STEREOSELECTIVE SYNTHESIS OF CYCLIC AMINO ACIDS



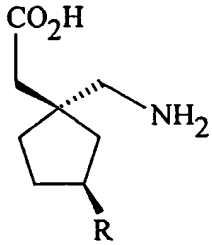
(A)



(I)



(II)



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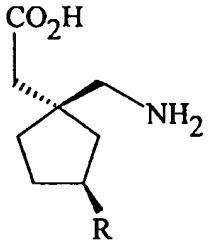


(IV)

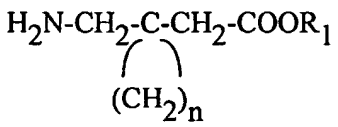
(57) Abstract: The instant invention is a route to stereospecific 3-substituted 5-membered ring isomers of Formula (A). The final products are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal disorders such as irritable bowel syndrome (IBS), inflammation especially arthritis, sleep disorders, premenstrual syndrome, and hot flashes. The invention provides novel routes to synthesize stereoselectively analogs of gabapentin (Neurontin®) of Formulas (I), (II), (III) and (IV) wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof.

WO 01/42190 A1

METHOD FOR THE STEREOSELECTIVE SYNTHESIS OF CYCLIC AMINO ACIDS

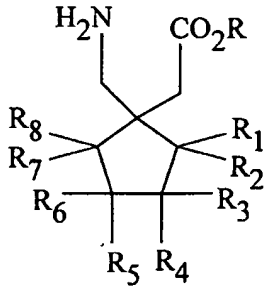
BACKGROUND OF THE INVENTION

Compounds of formula



wherein R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in United States Patent Number 4,024,175 and its divisional United States Patent Number 4,087,544. The uses disclosed are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The compounds are useful in geriatric patients. The patents are hereby incorporated by reference.

United States Serial Number 09/485,382 filed February 8, 2000 teaches in part compounds of Formula I

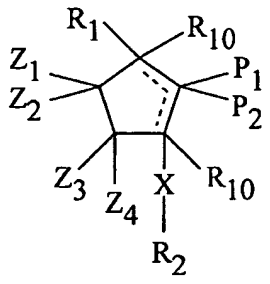


I

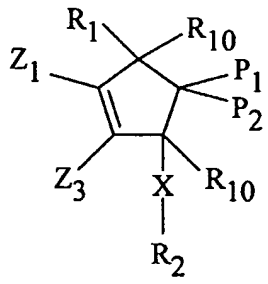
or a pharmaceutically acceptable salt thereof wherein R is hydrogen or a lower alkyl; and R_1 to R_8 are each independently selected from hydrogen, straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, benzyl, fluorine, chlorine, bromine, hydroxy, hydroxymethyl, amino, aminomethyl, trifluoromethyl, $-CO_2H$, $-CO_2R_{15}$, $-CH_2CO_2H$, $-CH_2CO_2R_{15}$, $-OR_{15}$ wherein R_{15} is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or benzyl, and R_1 to R_8 are not

simultaneously hydrogen. This patent application is hereby incorporated by reference.

United States Patent Number 5,929,116 describes endothelin antagonists of formulas

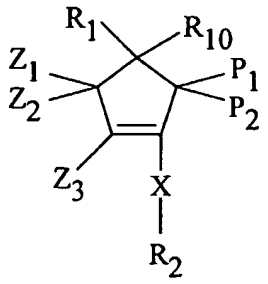


(I)



(II)

and



(III)

wherein

R_1 is $-X(CH_2)_nAr$;

R_2 is Ar;

P_1 is $-X(CH_2)_nR_8$;

P_2 is $-X(CH_2)_nR_8$, or $-XR_9Y$;

R_3 and R_5 are independently hydrogen, R_{11}, OH, C_{1-8} alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, Br, F, I, Cl, CF_3, $NHCOR_6$, $-R_{11}CO_2R_7$, $-XR_9$-Y, or $-X(CH_2)_nR_8$ wherein each methylene group within $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or two $-(CH_2)_nAr$ groups;

R_4 is hydrogen, R_{11}, OH, C_{1-5} alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, $-X(R_{11})$, Br, F, I, Cl, or $NHCOR_6$ wherein the C_{1-5} alkoxy may be unsubstituted or substituted by OH, methoxy, or halogen;

R_6 is independently hydrogen or C_{1-4} alkyl;

R_7 is independently hydrogen, C_{1-6} alkyl, or $(CH_2)_nAr$;

R_8 is hydrogen, R_{11}, CO_2R_7, PO_3H_2, $SO_2NR_7R_{11}$, $NR_7SO_2R_{11}$, $P(O)(OH)R_7$, CN, $-C(O)N(R_6)_2$, tetrazole, or OR_6;

R_9 is C_{1-10} alkyl, C_{2-10} alkenyl, or phenyl, all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, COOH, >C=O, halogen, or XC_{1-5} alkyl;

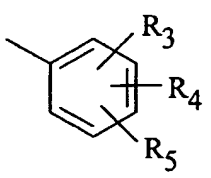
R_{10} is R_3 or R_4;

R_{11} is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, all of which may be unsubstituted or substituted by one or more OH, CH_2OH, $N(R_6)_2$, or halogen;

X is $(CH_2)_n$, O, NR_6, or $S(O)_q$;

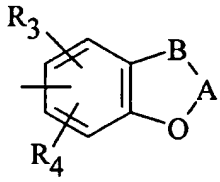
Y is CH_3 or $X(CH_2)_nAr$;

Ar is:



(a)

or



(b)

or

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is >C=O, or $[C(R_6)_2]_m$;

B is $-CH_2-$ or -O-;

Z_1, Z_2, Z_3, and Z_4 are independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, OH, C_{1-8} alkoxy, $S(O)_qC_{1-8}$ alkyl, $N(R_6)_2$, Br, F, I, Cl, $NHCOR_6$, $-X(CH_2)_nR_8$, XR_9Y, phenyl, benzyl, or C_{3-6} cycloalkyl wherein the C_{1-8} alkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl may be optionally substituted by COOH, OH, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R_6)_2$, or halogen;

q is zero, one, or two;

n is an integer from 0 to 6;

m is 1, 2, or 3;

and the dotted line in Formula (I) indicates the optional presence of a double bond; or a pharmaceutically acceptable salt thereof; provided that

- when the optional double bond is present, there is only one R_{10}, there is no P_1, and P_2 is not NR_6R_9Y;

- X is not NR_6, and Z_3 is not OH or $N(R_6)_2$ in Formula (III);
- Z_1 and Z_3 are not OH, $N(R_6)_2$, or Iodine in Formula (II);
- when the optional double bond is present in Formula (I) and X-R_2 is attached to the double bond, X is not NR_6;
- when the optional double bond is present in Formula (I) and R_1 is attached directly to the double bond, R_1 is not NR_6Ar;
- when R_3, R_5, Z_1, Z_2, or Z_3 is $X(CH_2)_nR_8$ and n is not zero, X is oxygen or NR_6 when R_8 is OR_6 or CO_2H.

Also included in the invention are pharmaceutically acceptable salts of the active compounds.

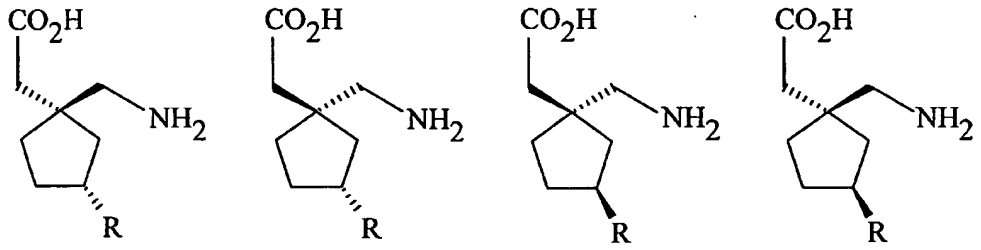
Most or all of the desired pharmacological activity of a compound comprised of two or more stereoisomers frequently resides in just one of the stereoisomers. The other stereoisomer(s) typically is inactive at best or exhibits undesirable side effects such as, for example, toxicity. Therefore where a compound is comprised of two or more stereoisomers, it is important, and sometimes mandatory, to develop a method of selectively preparing the beneficial stereoisomer in a form that is free from, or almost free from, contamination by the other inactive or harmful stereoisomer(s). However, usually it is very difficult to discover a method for the preparation of a beneficial stereoisomer in a form that is free from, or almost free from, contamination by the other inactive or harmful stereoisomer(s). Unexpectedly, we have invented novel preparations of certain important 3-substituted cyclopentyl-containing, amino acid analogs of gabapentin, a marketed anticonvulsant, which provide the desirable stereoisomers with a high degree of stereochemical purity.

None of the above teach the synthesis of the instant invention.

SUMMARY OF THE INVENTION

The instant invention encompasses novel synthetic routes for the preparation of important 3-substituted cyclopentyl-based analogs of gabapentin and pharmaceutically acceptable salts thereof. Gabapentin, marketed under the

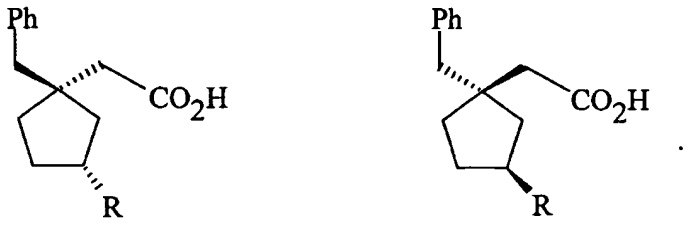
trade name Neurontin® for the treatment of seizure disorders, particularly epilepsy, provides well-known medical benefits to patients in need of such treatment. The instant invention encompasses novel synthetic routes for the preparation of 3-substituted cyclopentyl-based analogs of gabapentin and pharmaceutically acceptable salts thereof that enable the synthesis of each stereoisomer of these analogs with a high degree of stereochemical purity. These routes provide access to pure stereoisomers of Formulas I, II, III, and IV



I II III IV

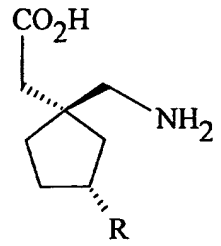
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl.

Further, the invention encompasses the key intermediates of formulas (6) and (26). Still further, the invention provides novel synthetic routes for the preparation of compounds of formulas (6) and (26). The routes enable the synthesis of each stereoisomer of compounds of formulas (6) and (26) with a high degree of stereochemical purity. These routes provide access to pure stereoisomers of formulas (6) and (26) wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl.



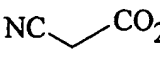
(6) (26)

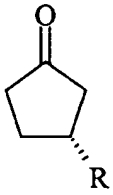
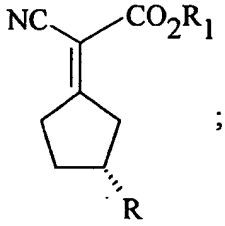
The invention provides a process for the preparation of a compound of Formula I



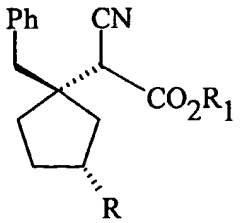
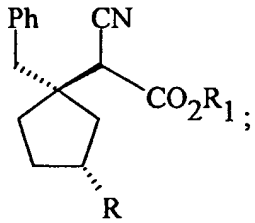
I

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

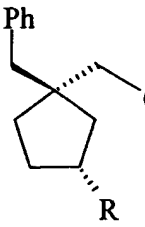
a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (1)

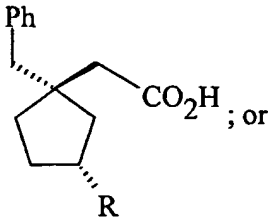
 , a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (2)  ;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition products of formulas (3a)

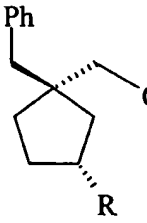
 and (3b)  ;

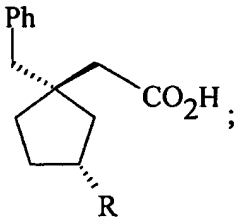
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, or cesium hydroxide in a solvent and stirring, and then acidifying to produce the

carboxylic acids of formulas (4a)  and (4b)

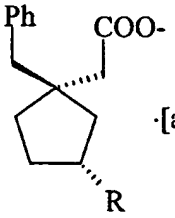


adding the products of Step b) above to an acid mixture and stirring to

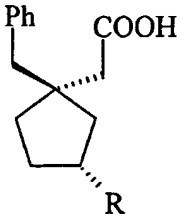
produce the carboxylic acids of formulas (4a)  and (4b)

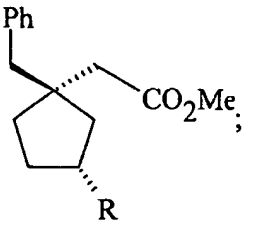


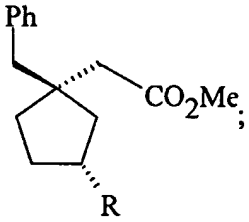
d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of

formula (5)  ·[amine-H]$^+$ as the amine salt;

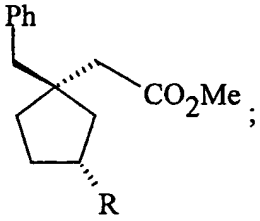
e) converting the product of Step d) to a carboxylic acid of formula (6)



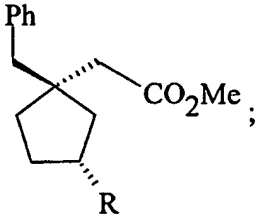
f) adding the product of Step e) to a mixture of iodomethane, a solvent, and a base, and stirring to produce the ester of formula (7)  ;

or adding the product of Step e) to methanol and an acid to produce the ester of formula (7)  ;

or adding the product of Step e) above to trimethylsilyldiazo-methane and methanol in a solvent to produce the ester of formula (7)

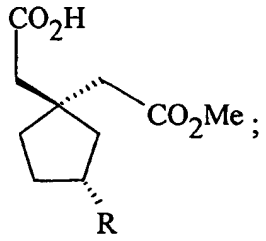
 ;

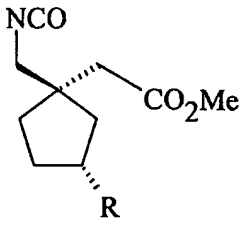
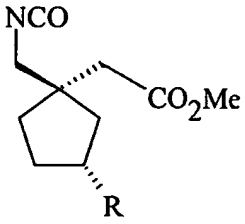
or adding the product of Step e) to a solution of diazomethane or trimethylsilyl-diazomethane in a solvent to produce ester of formula (7)

 ;

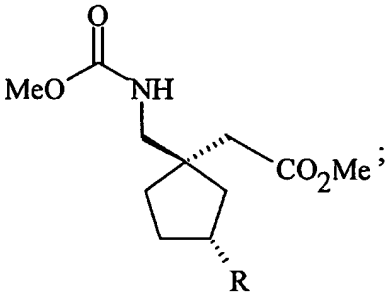
g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III)

chloride, and stirring to produce the carboxylic acid of formula (8)

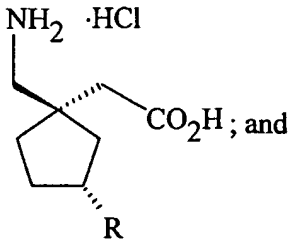


h) adding the product of Step g) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the isocyanate of formula (9)  ; or adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate of formula (9)  ;

i) adding the product of Step h) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (10)

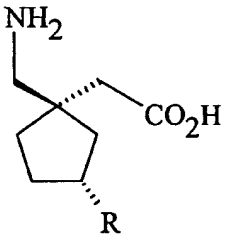


j) adding the product of Step i) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (Ia)



; and

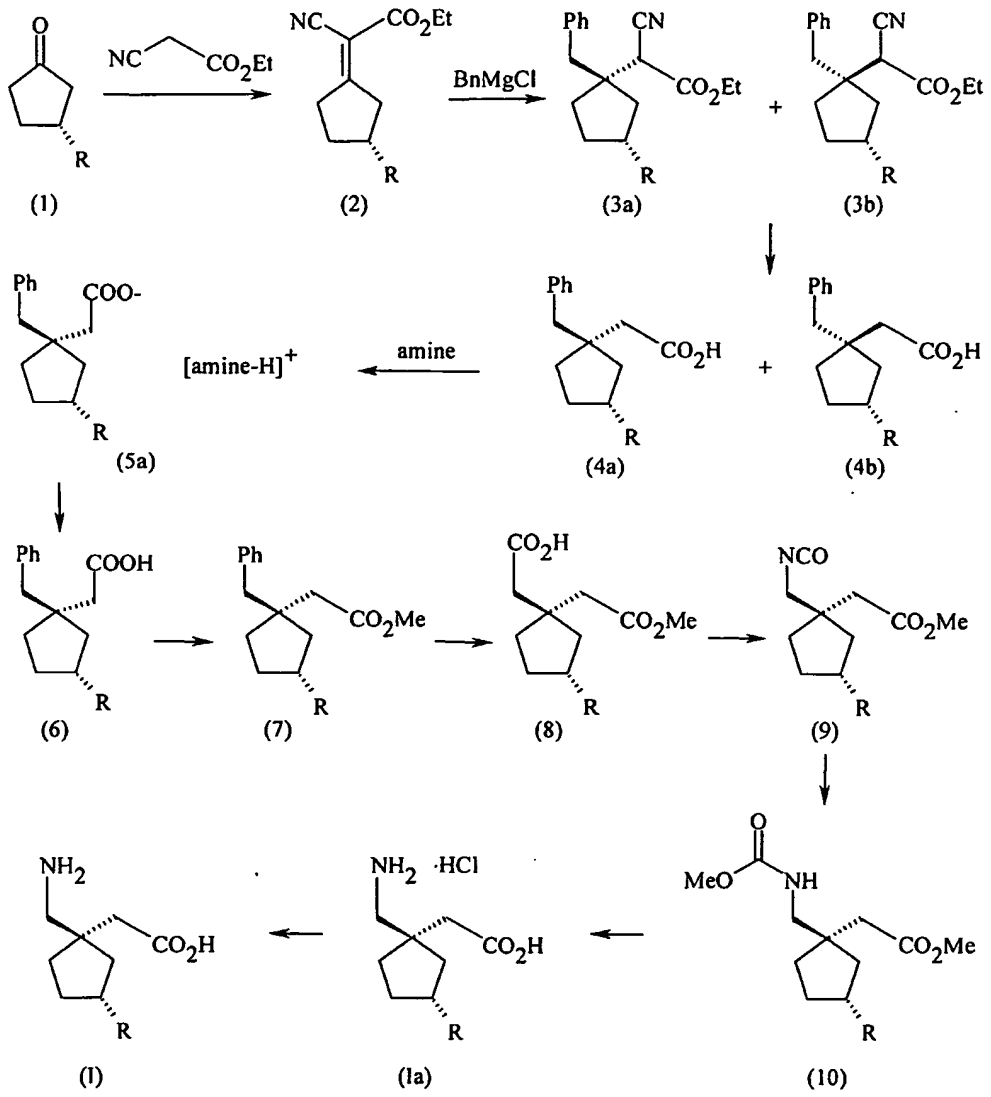
k) converting the product of Step j) to a compound of formula (I)



, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

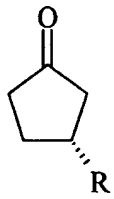
This process is outlined in Scheme 1.

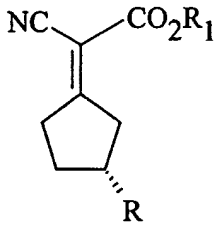
Scheme 1

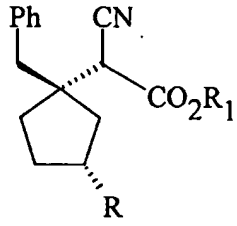


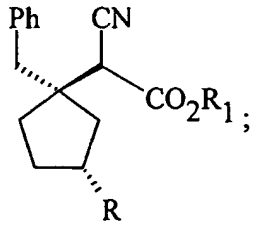
Preferred is a process for the preparation of a compound of Formula I wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A) $NC\diagup\!\!\diagdown CO_2R_1$ wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of

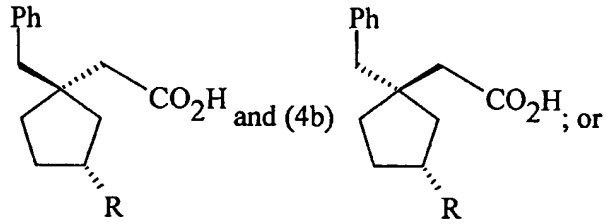
formula (1)  , a solvent selected from tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

 ;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce the addition products of formulas (3a)  and

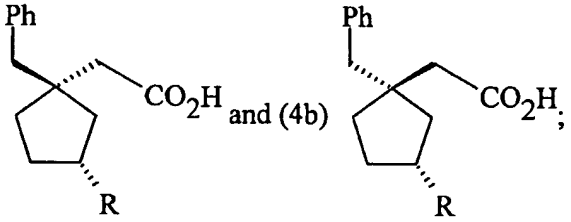
(3b)  ;

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture, and then acidifying to produce the carboxylic acids of formulas (4a)

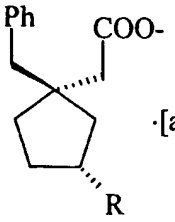


adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H_2SO_4, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of

formulas (4a)

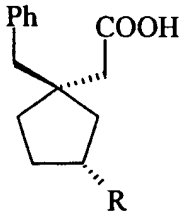


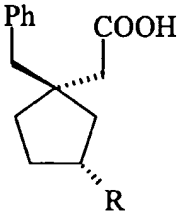
d) contacting the products of Step c) above with an amine selected from (S)-α-methyl-benzylamine, (R)-α-methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to

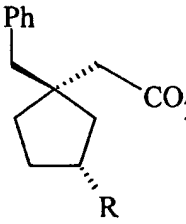
produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$

as the amine salt;

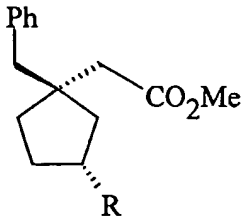
e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid to which water is added and stirring to produce the carboxylic acid of

formula (6)  ; or

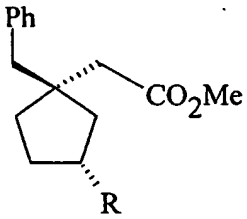
partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of formula (6)  ;

f) adding the product of Step e) above to a mixture of iodomethane, a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene, and 1,4-dioxane, and a base selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine, triethylamine, and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and stirring at a temperature of from -40°C to 110°C to produce the ester of formula (7)  ;

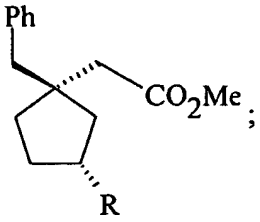
or adding the product of Step e) above to a mixture of methanol and concentrated sulphuric acid, concentrated hydrochloric acid, or hydrogen chloride at a temperature of from 0°C to 100°C to produce the ester of

formula (7)  ; or adding the product of Step e) above to

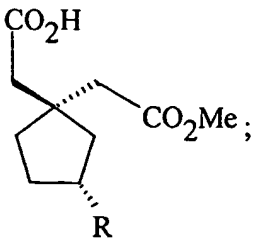
trimethylsilyldiazomethane and methanol in benzene or toluene at a temperature of from -40°C to 100°C to produce the ester of formula (7)

 ; or adding the product of Step e) above to

diazomethane or trimethylsilyldiazomethane in a solvent selected from benzene, toluene, dichloromethane, and diethyl ether at a temperature of from -40°C to 40°C to give a compound of formula (7)

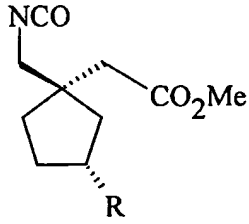
 ;

g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to 80°C to produce the

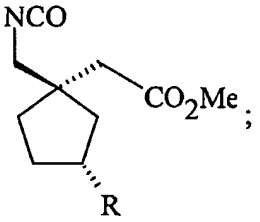
carboxylic acid of formula (8)  ;

h) adding the product of Step g) above to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene,

benzene, xylenes, tetrahydrofuran, diethyl ether and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature of from 0°C to 150°C to produce the isocyanate of formula (9)

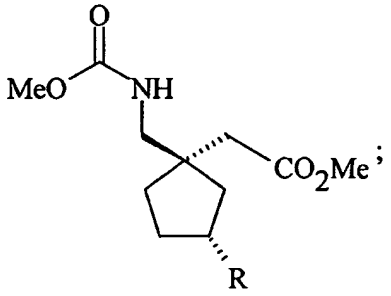


; or adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate, a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate of formula (9)



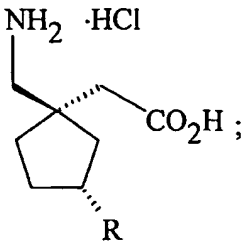
;

i) adding the product of Step h) to a mixture of a solvent selected from toluene, benzene, xylenes and *n*-heptane, and methanol, and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (10)



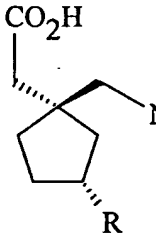
;

j) adding the product of Step i) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from

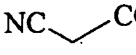
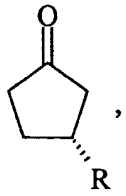
0°C to 115°C to produce a compound of formula Ia  ;

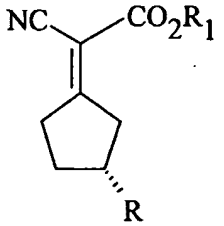
and

k) converting the product of Step j) to a compound of Formula I

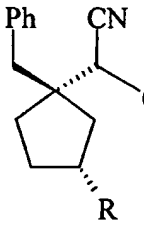
 , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

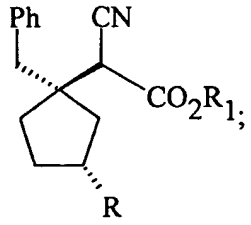
More preferred is a process for the preparation of a compound of Formula I wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A)  , wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)  ,

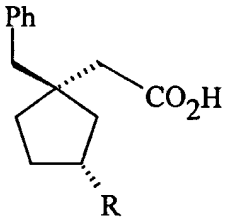
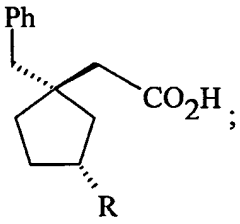
toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)  ;

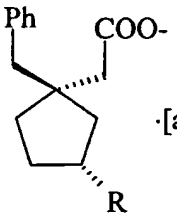
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition

products of formulas (3a)  and (3b)

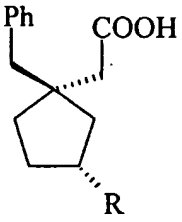
 ;

c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of

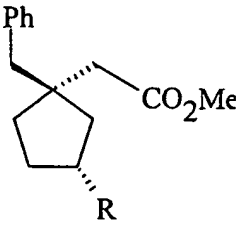
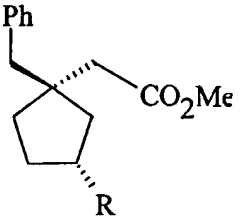
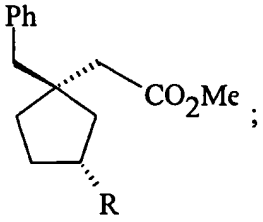
formulas (4a)  and (4b)  ;

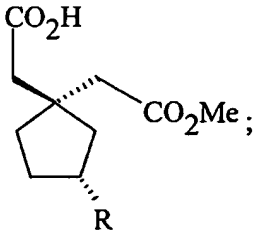
d) contacting the products of Step c) above with (S)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$

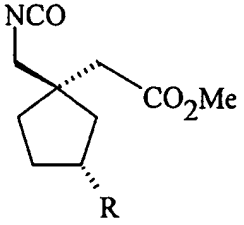
as the (S)-α-methyl-benzylamine salt;

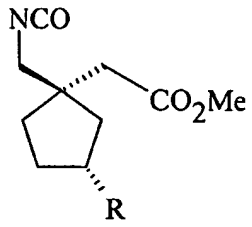
e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (6)  ;

f) adding the product of Step e) to a mixture of iodomethane, dichloromethane, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and

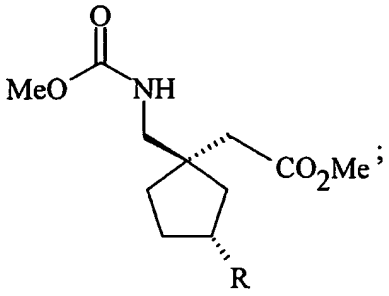
stirring to produce the ester of formula (7)  ; or adding the product of Step e) to methanol and concentrated sulfuric acid to produce the ester of formula (7)  ; or adding the product of Step e) to a solution of diazomethane or trimethylsilyl-diazomethane in dichloromethane to produce the ester of formula (7)  ;

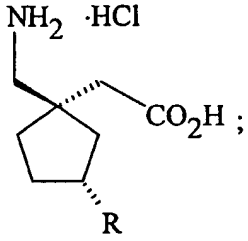
g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (8)  ;

h) adding the product of Step g) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the isocyanate of formula (9)  ; or adding the product of

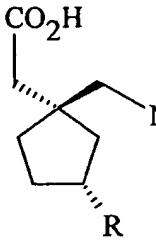
Step g) above to ethyl chloroformate or isobutyl chloroformate and triethylamine in tetrahydrofuran at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran, followed by adding toluene or benzene, and refluxing to produce ester of formula (9)  ;

i) adding the product of Step h) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (10)

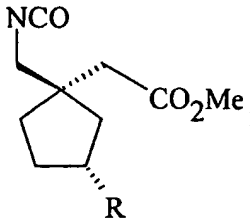


j) adding the product of Step i) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a compound of formula Ia  ;

k) converting the product of Step j) to a compound of Formula I

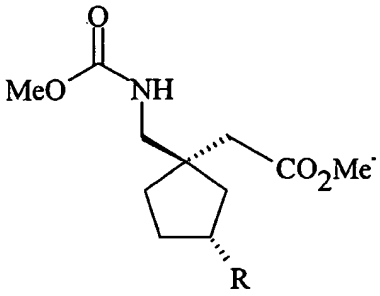
 , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

Also preferred is a process for the preparation of a compound of Formula I as described above, further characterized in that the intermediate

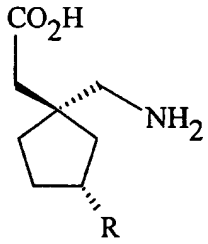


product (9) formed is reacted, without isolation, with

methanol to produce the carbamate of formula (10)

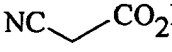


Further, the invention provides a process for the preparation of a compound of Formula II

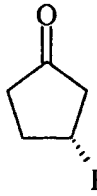


II

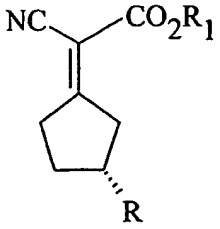
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

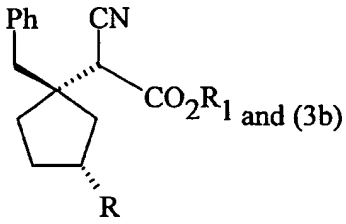
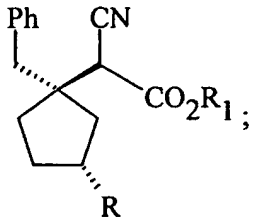
a) adding a cyanoacetate of formula (A) 

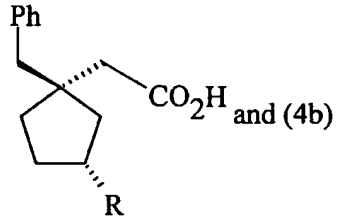
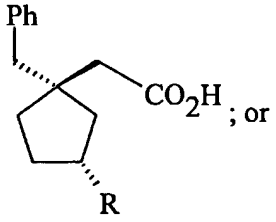
, wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of

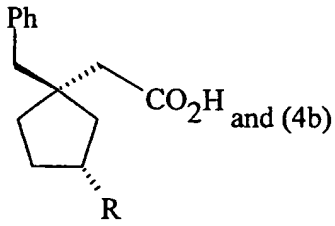
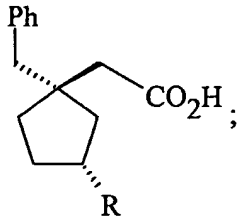
formula (1) 

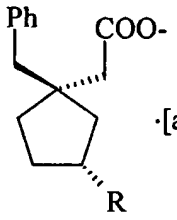
, a solvent, a carboxylic acid, and a Knoevenagel

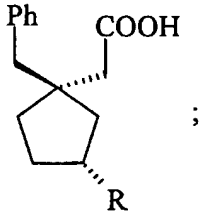
reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (2)  ;

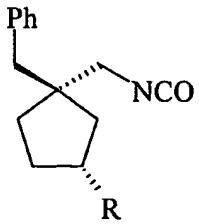
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition products of formulas (3a)  and (3b)  ;

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide and a solvent, and stirring, and then acidifying to produce the carboxylic acids of formulas (4a)  and (4b)  ; or

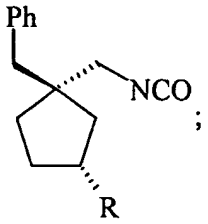
adding the products of Step b) above to an acid mixture and stirring to produce the carboxylic acids of formulas (4a)  and (4b)  ;

d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$ as the amine salt; and

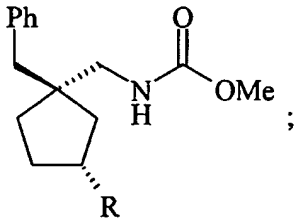
e) converting the product of Step d) to a carboxylic acid of formula (6)  ;

f) adding the product of Step e) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the isocyanate of formula (11)  ; or adding the product of Step e) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed

by adding toluene or benzene, and refluxing to produce isocyanate of

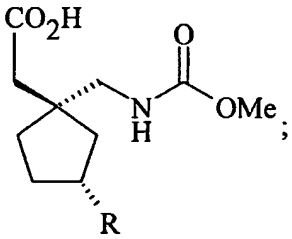
formula (11) 

;

g) adding the product of Step f) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (12) 

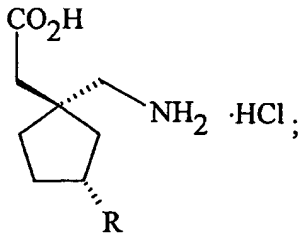
;

h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of

formula (13) 

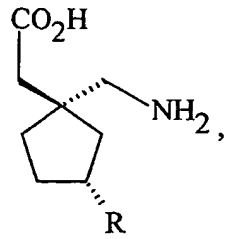
;

i) adding the product of Step h) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (IIa)



;

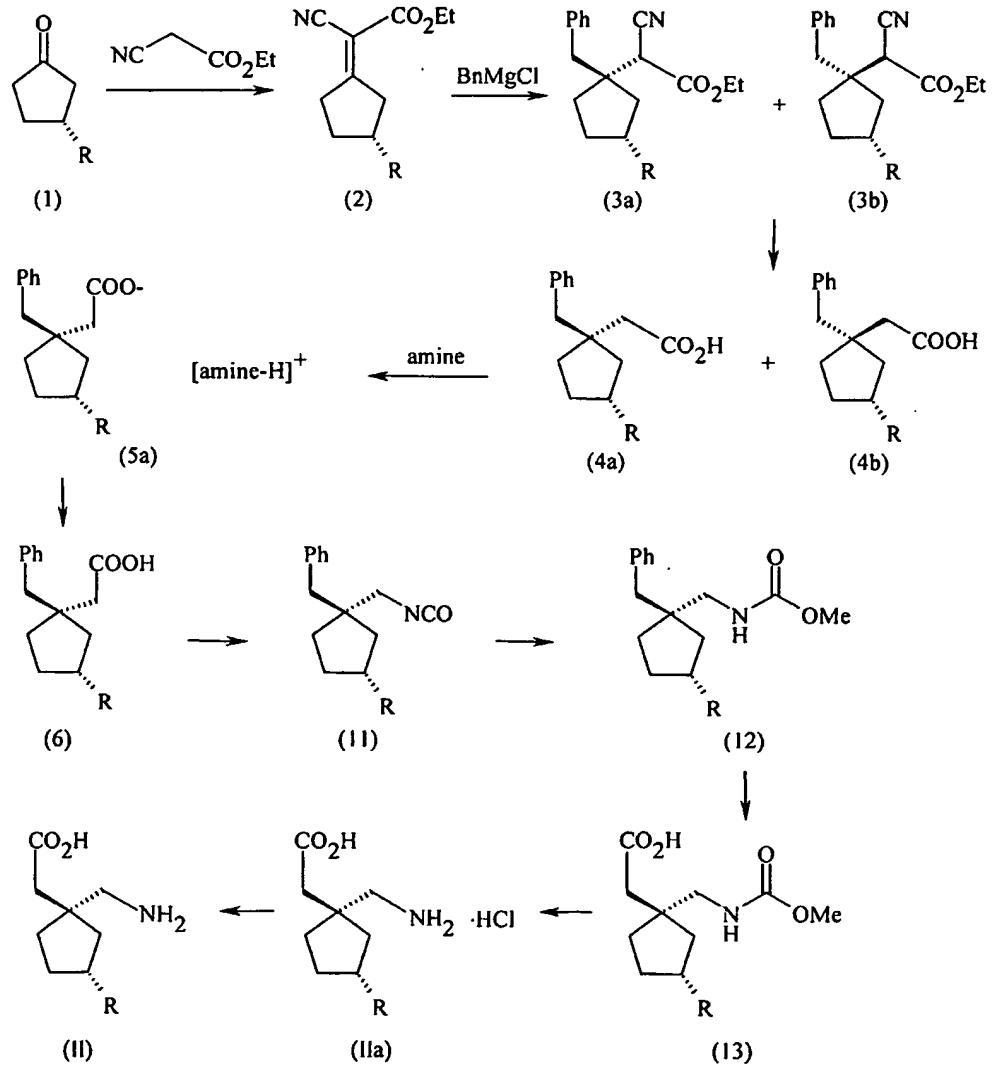
j) converting the product of Step i) to a compound of formula (II)



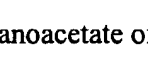
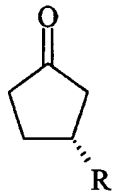
, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

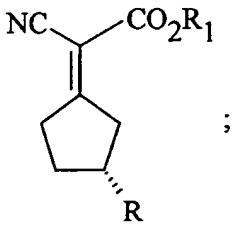
This process is outlined below in Scheme 2.

Scheme 2

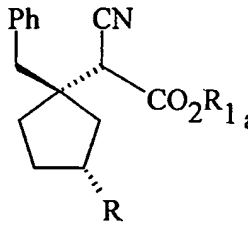


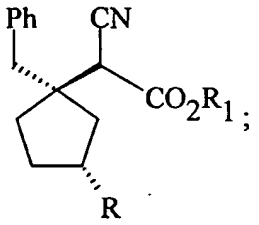
Preferred is a process for the preparation of a compound of Formula II wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A)  wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of formula (1)  , a solvent selected from tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

 ;

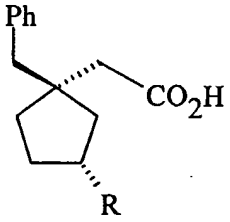
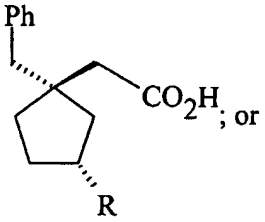
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce

the addition products of formulas (3a)  and

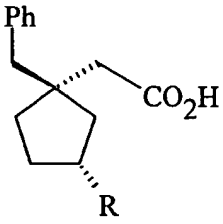
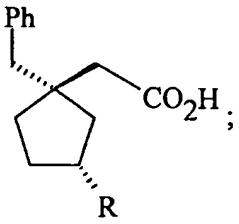


(3b) ;

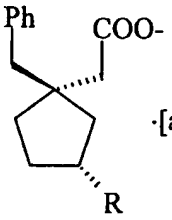
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture and then acidifying to produce the carboxylic acids of formulas (4a)

 and (4b)  ; or

adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H_2SO_4, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of

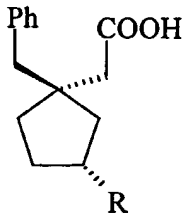
formulas (4a)  and (4b)  ;

d) contacting the products of Step c) above with an amine selected from (S)-α-methyl-benzylamine, (R)-α-methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and

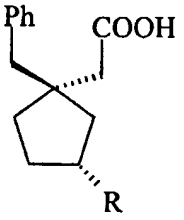
pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (5) 

·[amine-H]$^+$ as the amine salt;

e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid dissolved in acetic acid and water, and stirring to produce the carboxylic acid of formula (6)

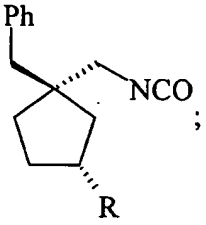


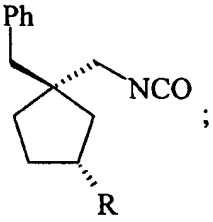
; or

partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of formula (6) 

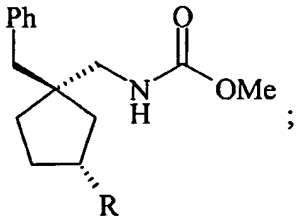
;

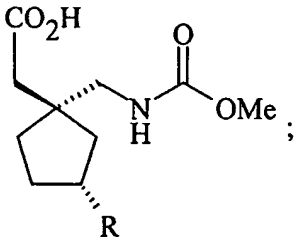
f) adding the product of Step e) above to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene, benzene, xylenes, tetrahydrofuran, diethyl ether and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature of from

0°C to 150°C to produce the isocyanate of formula (11)  ;

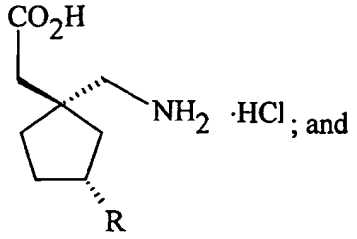
or adding the product of Step e) above to ethyl chloroformate or isobutyl chloroformate and a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate of formula (11)  ;

g) adding the product of Step f) to a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and methanol, and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (12)

 ;

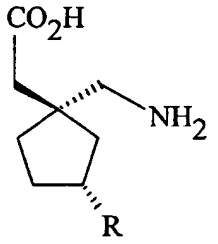
h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (13)  ;

i) adding the product of Step h) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from 0°C to 115°C to produce a compound of formula IIa



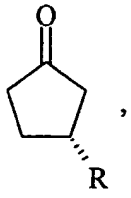
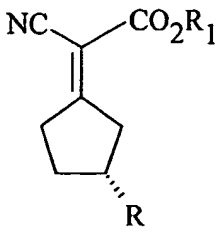
; and

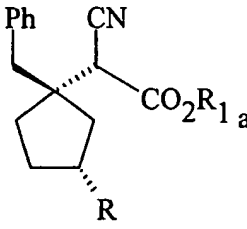
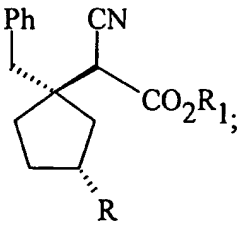
j) converting the product of Step i) to a compound of Formula II

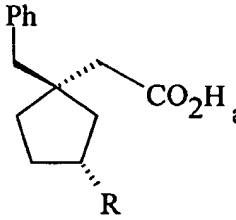
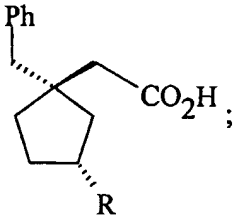


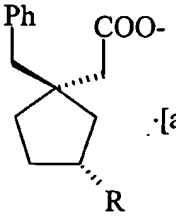
, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

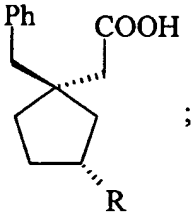
More preferred is a process for the preparation of a compound of Formula II wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A) , wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)  , toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)  ;

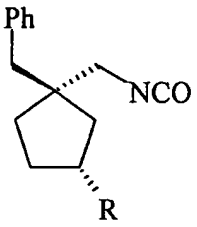
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition products of formulas (3a)  and (3b)  ;

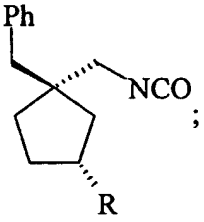
c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of formulas (4a)  and (4b)  ;

d) contacting the products of Step c) above with (S)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$ as the (S)-α-methyl-benzylamine salt;

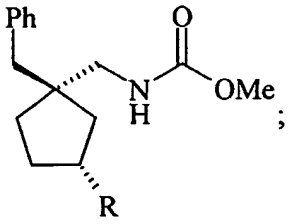
e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (6)  ;

f) adding the product of Step e) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the

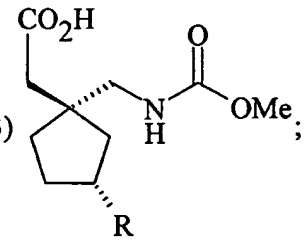
isocyanate of formula (11)  ; or adding the product of

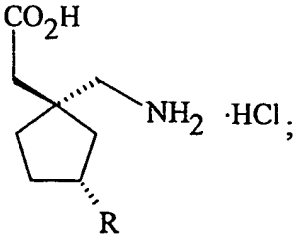
Step e) above to ethyl chloroformate or isobutyl chloroformate and triethylamine in tetrahydrofuran at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (11)  ;

g) adding the product of Step f) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (12)

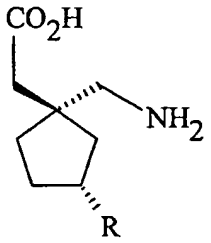
 ;

h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of

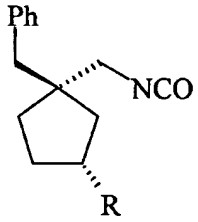
formula (13)  ;

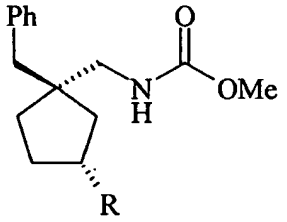
i) adding the product of Step h) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a compound of formula IIa 

;

j) converting the product of Step i) to a compound of Formula II 

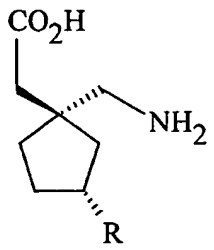
, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

Also preferred is a process for the preparation of a compound of Formula II as described above, further characterized in that the intermediate product (11) 

formed is further reacted, without isolation, with methanol to produce the carbamate of formula (12) 

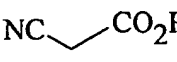
.

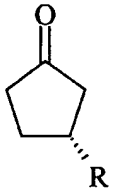
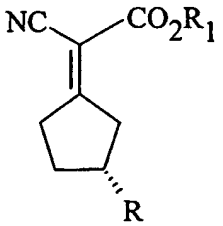
Still further, the invention provides a process for the preparation of a compound of Formula II



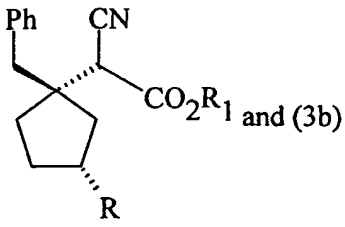
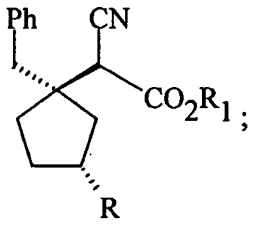
II

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

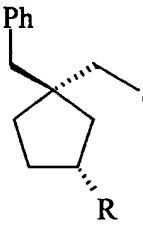
a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (1)

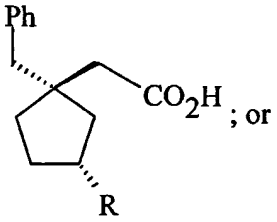
 , a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (2)  ;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition products of formulas (3a)

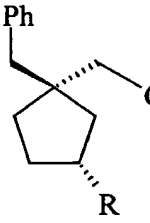
 and (3b)  ;

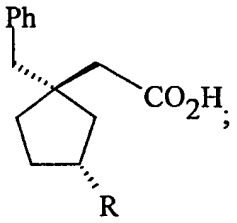
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying to produce the

carboxylic acids of formulas (4a)  and (4b)

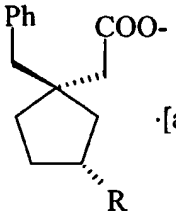


adding the products of Step b) above to an acid mixture and stirring to

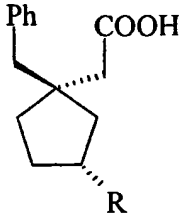
produce the carboxylic acids of formulas (4a)  and (4b)

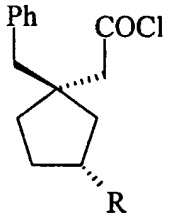


d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of

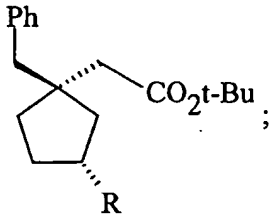
formula (5)  ·[amine-H]$^+$ as the amine salt;

e) converting the product of Step d) to a carboxylic acid of formula (6)

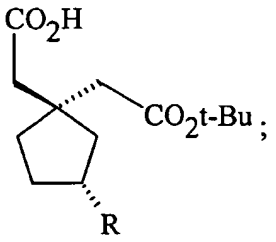


f) adding oxalyl chloride to a mixture of the product of Step e), a solvent, and N,N-dimethylformamide (DMF), and stirring to produce the acid chloride of formula (14) 

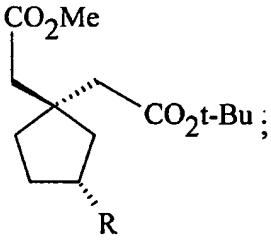
;

g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent, and a tertiary amine base, and stirring to produce the ester of formula (15) 

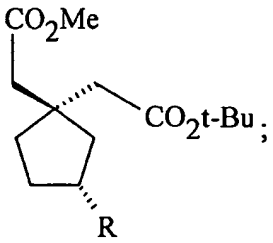
;

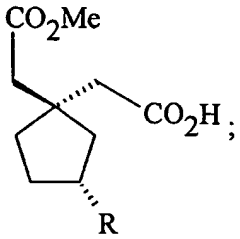
h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (16) 

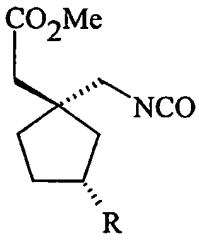
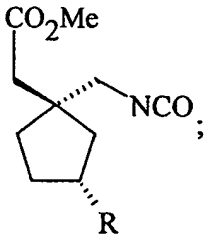
;

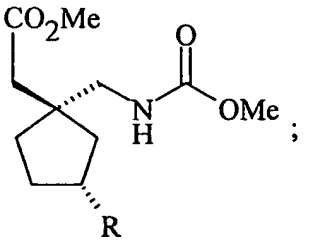
i) adding the product of Step h) to a mixture of a solvent, methanol, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of formula (17) 

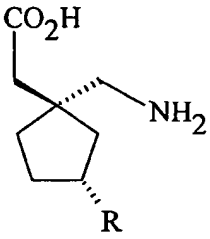
; or adding the product of Step h) to a

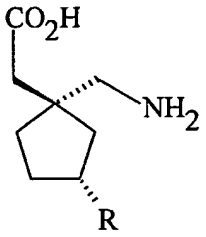
mixture of iodomethane, a solvent, and a base, and stirring to produce the bis ester of formula (17)  ;

j) adding an acid to a mixture of the product from Step i) and a solvent, and stirring to produce the carboxylic acid of formula (18)  ;

k) adding the product of Step j) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA) is added, and stirring to produce the isocyanate of formula (19)  ; or adding the product of Step j) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (19)  ;

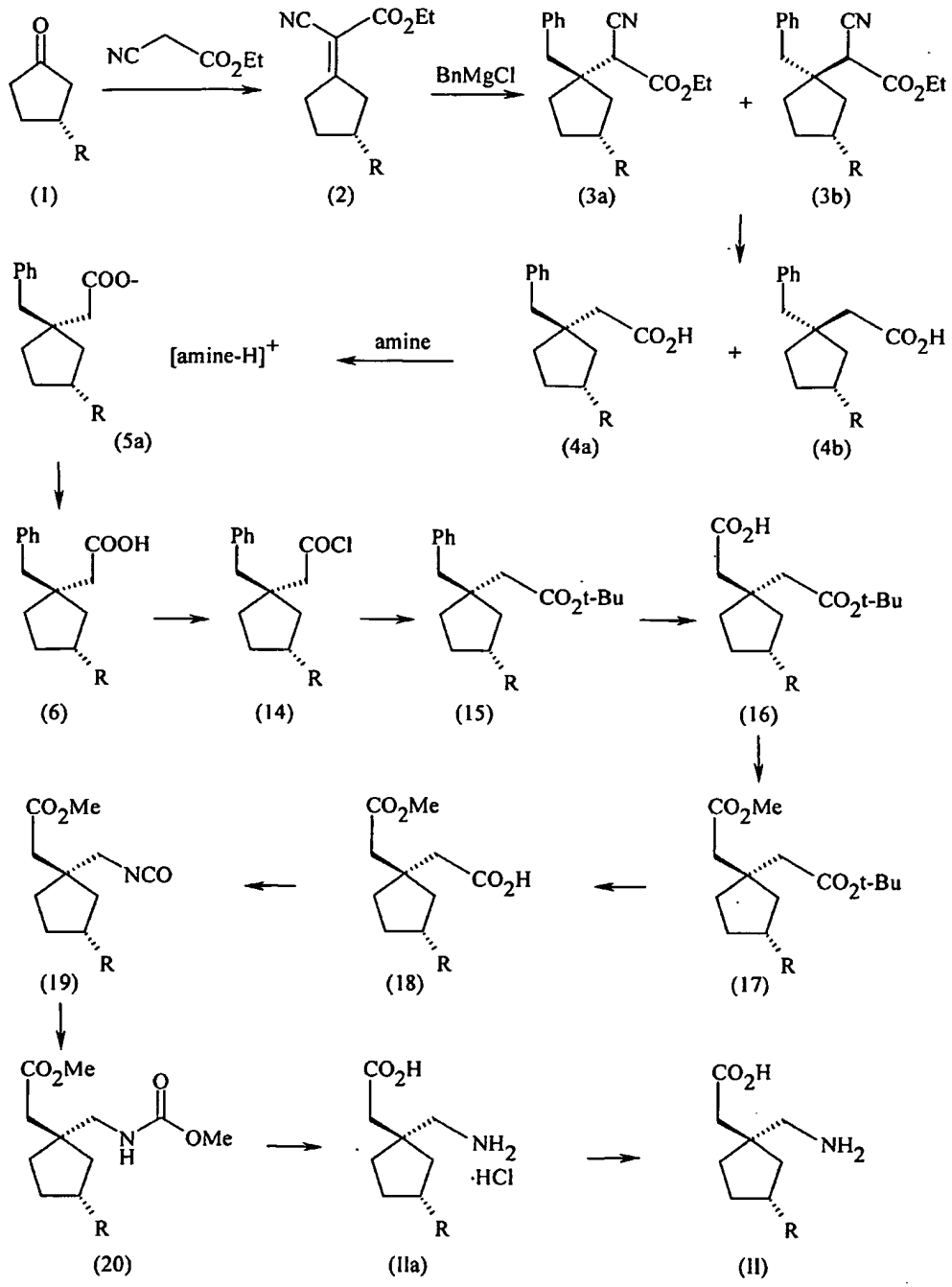
l) adding the product of Step k) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (20)  ;

m) adding the product of Step l) to a mixture of a solvent and aqueous hydrochloric acid is added, and stirring to produce a compound of formula (IIa)  ; and

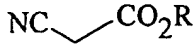
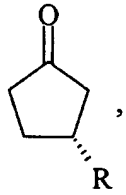
n) converting the product of Step m) to a compound of formula (II)  , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

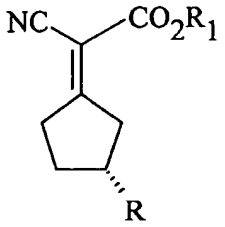
This process is outlined in Scheme 3.

Scheme 3

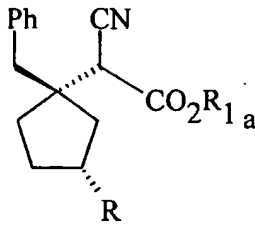


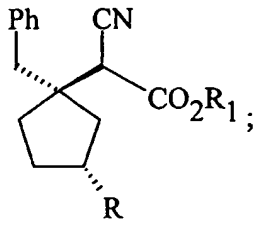
Preferred is a process for the preparation of a compound of Formula II wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A)  wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of formula (1)  , a solvent selected from tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

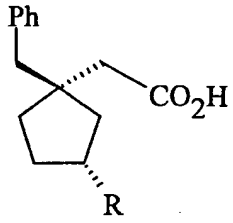
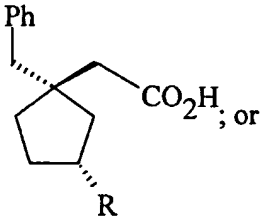
 ;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce

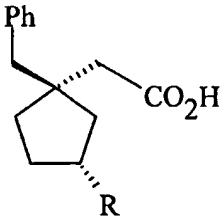
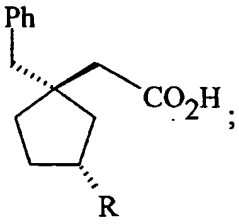
the addition products of formulas (3a)  and (3b)

 ;

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture and then acidifying to produce the carboxylic acids of formulas (4a)

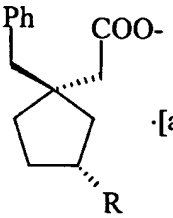
 and (4b)  ; or

adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H_2SO_4, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of

formulas (4a)  and (4b)  ;

d) contacting the products of Step c) above with an amine selected from (S)-α-methyl-benzylamine, (R)-α-methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and

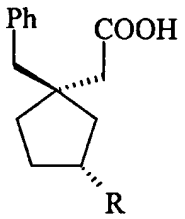
pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (5)



·[amine-H]$^+$

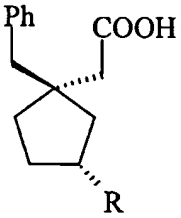
as the amine salt;

e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid and water, and stirring to produce the carboxylic acid of formula (6)



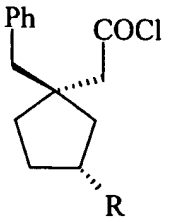
; or

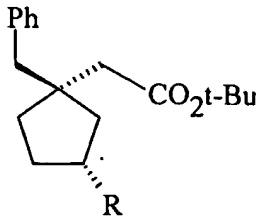
partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of formula (6)

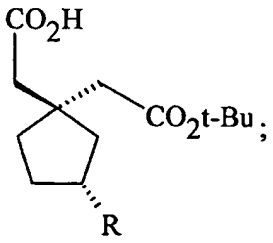


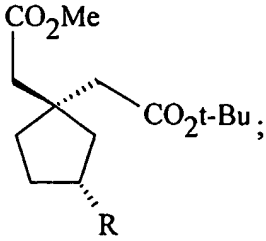
;

f) adding oxalyl chloride to a mixture of the product of Step e), a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, and *tert*-butyl methyl ether, and 0.01 to 10 mole percent of N,N-

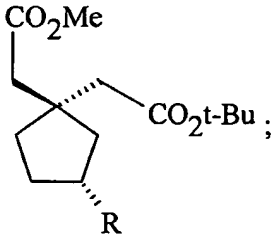
dimethylformamide (DMF), and stirring at a temperature from -40°C to 110°C to produce the acid chloride of formula (14)  ;

g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, and *tert*-butyl methyl ether, and *N,N*-diisopropylethylamine (DIPEA) or triethylamine, and stirring at a temperature from -40°C to 110°C to produce the ester of formula (15)  ;

h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (16)  ;

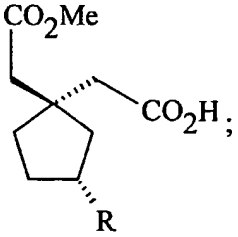
i) adding the product of Step h) to a solvent selected from toluene, benzene, xylenes, and *n*-heptane, methanol, and (trimethylsilyl)diazomethane, and stirring at a temperature from 0°C to 150°C to produce the bis ester of formula (17)  ; or adding the product of Step h) to a mixture of iodomethane, a solvent selected from dichloromethane,

chloroform, tetrahydrofuran, toluene and 1,4-dioxane, and a base selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine, triethylamine, or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and stirring at a temperature of from -40°C to 110°C to produce the bis ester of

formula (17) 

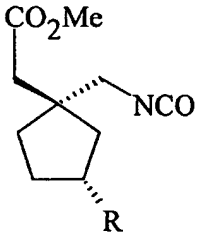
;

j) adding hydrochloric acid or trifluoroacetic acid (TFA) to a mixture of the product from Step i) and a solvent selected from dichloromethane, chloroform, 1,4-dioxane, tetrahydrofuran, ethyl ether, and *tert*-butyl methyl ether, and stirring at a temperature from -40°C to 110°C to produce

the carboxylic acid of formula (18) 

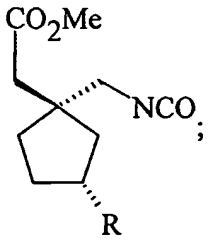
;

k) adding the product of Step j) to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature from 0°C to 150°C to produce the isocyanate

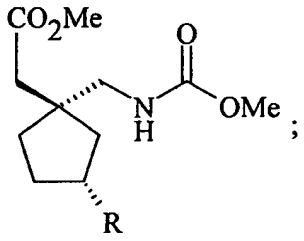
of formula (19) 

; or adding the product of Step j) above to

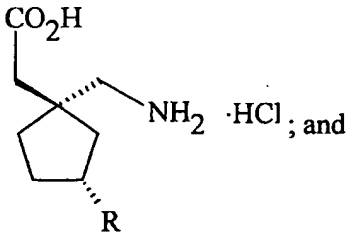
ethyl chloroformate or isobutyl chloroformate, a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and

tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (19)  ;

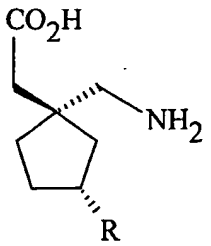
l) adding the product of Step k) to a mixture of a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and methanol, and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (20)

 ;

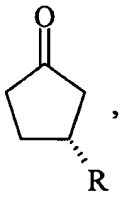
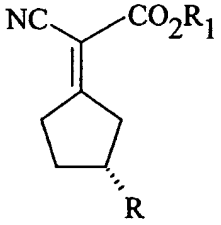
m) adding the product of Step l) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from 0°C to 115°C to produce a compound of formula IIa

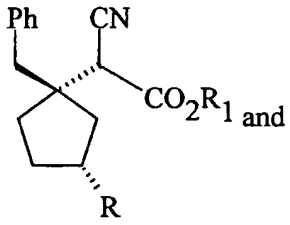
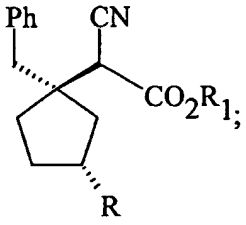
 ; and

n) converting the product of Step m) to a compound of Formula II

 , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

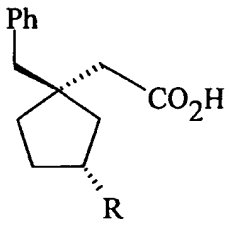
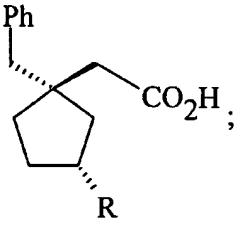
More preferred is a process for the preparation of a compound of Formula II wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

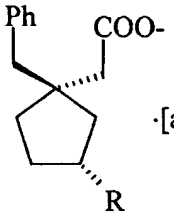
a) adding a cyanoacetate of formula (A) , wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)  , toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)  ;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition products of formulas (3a)  and (3b)  ;

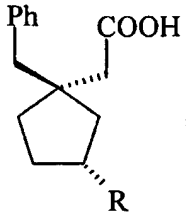
c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol and heating the mixture at 100°C to 200°C, and then

acidifying to produce the hydrolysis products of formulas

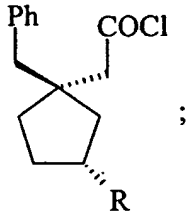
(4a)  and (4b)  ;

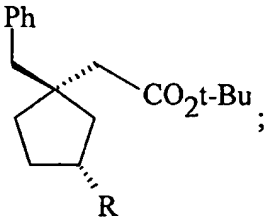
d) contacting the products of Step c) above with (S)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$

as the (S)-α-methyl-benzylamine salt;

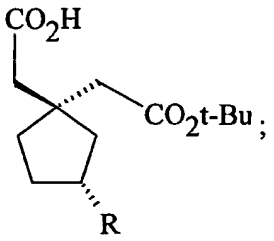
e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (6)  ;

f) adding oxalyl chloride to a mixture of the product of Step e), dichloromethane, and a catalytic amount of N,N-dimethylformamide (DMF), and stirring to produce the acid chloride of formula (14)

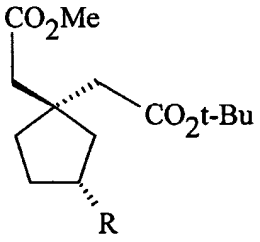
 ;

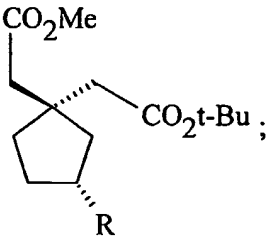
g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, dichloromethane, and *N,N*-diisopropylethylamine (DIPEA), and stirring to produce the ester of formula (15) 

;

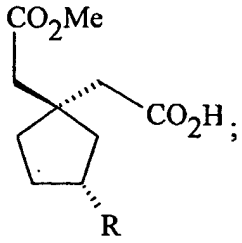
h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (16) 

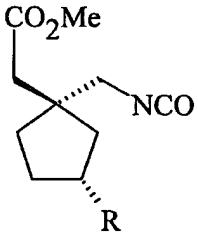
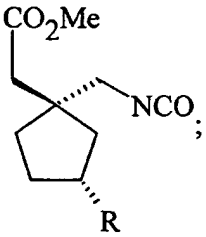
;

i) adding the product of Step h) to a mixture of methanol, toluene, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of formula (17) 

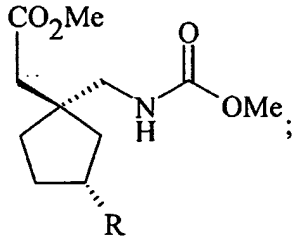
; or adding the product of Step h) to a mixture of iodomethane, dichloromethane, triethylamine, and stirring to produce the bis ester of formula (17) 

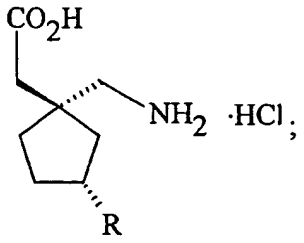
;

j) adding hydrochloric acid or trifluoroacetic acid (TFA) to a mixture of the product from Step i) and dichloromethane, and stirring to produce the carboxylic acid of formula (18)  ;

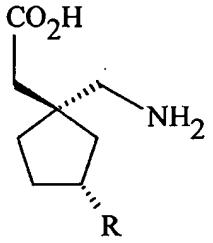
k) adding the product of Step j) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the isocyanate of formula (19)  ; or adding the product of Step j) above to ethyl chloroformate or isobutyl chloroformate, triethylamine, and tetrahydrofuran at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (19)  ;

l) adding the product of Step k) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (20)

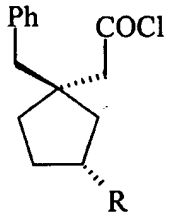


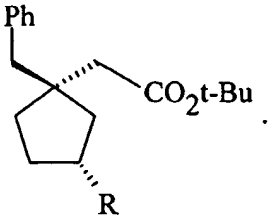
m) adding the product of Step l) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a compound of formula IIa 

;

n) converting the product of Step m) to a compound of Formula II 

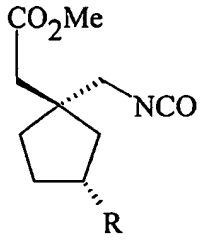
, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

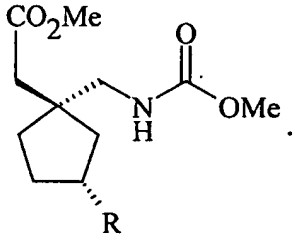
Also preferred is a process for the preparation of a compound of Formula II, further characterized in that the intermediate product (14) 

formed is further reacted, without isolation, with *tert*-butyl alcohol to produce the ester of formula (15) 

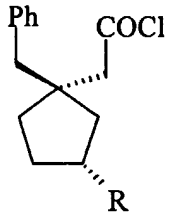
.

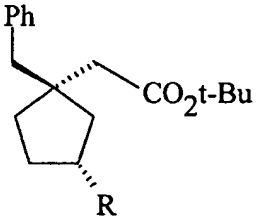
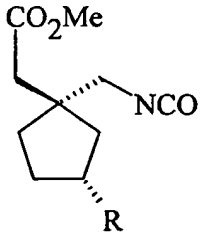
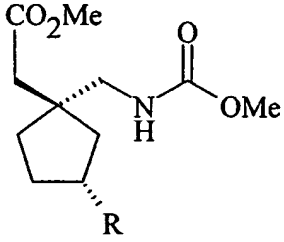
Also preferred is a process for the preparation of a compound of Formula II, further characterized in that the intermediate product (19)



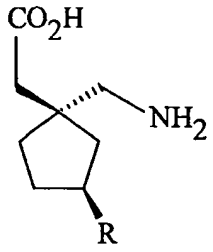
formed is further reacted, without isolation, with methanol to produce the carbamate of formula (20)  .

Also preferred is a process for the preparation of a compound of Formula II, further characterized in that the intermediate product (14)



formed is further reacted, without isolation, with *tert*-butyl alcohol to produce the ester of Formula (15)  , and the intermediate product (19)  formed is further reacted, without isolation, with methanol to produce the carbamate of formula (20)  .

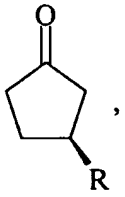
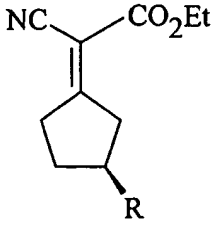
Further, the invention provides a process for the preparation of a compound of Formula III



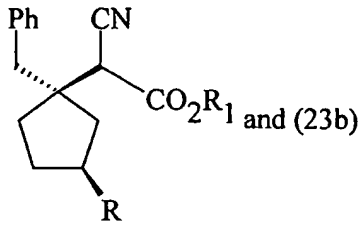
III

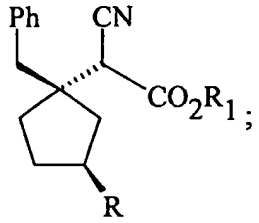
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)

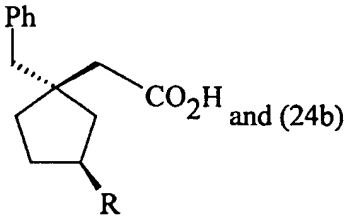
 , a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (22)  ;

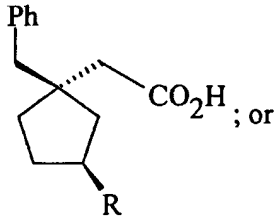
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition

of products of formulas (23a)  and (23b)

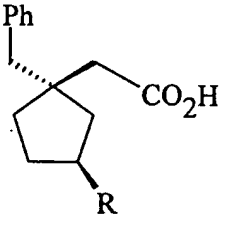
 ;

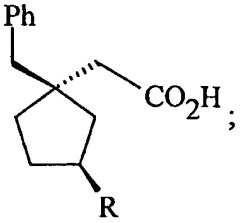
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying to produce the

carboxylic acids of formulas (24a)  and (24b)

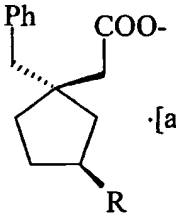
 ; or

adding the products of Step b) above to an acid mixture, and stirring to

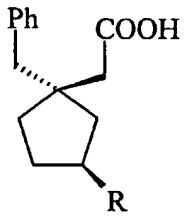
produce the carboxylic acids of formulas (24a) 

and (24b)  ;

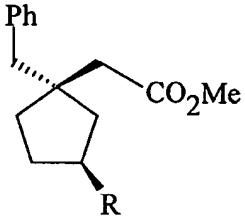
d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of

formula (25)  ·[amine-H]$^+$ as the amine salt; and

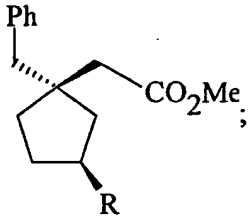
e) converting the product of Step d) to a carboxylic acid of formula (26)

 ;

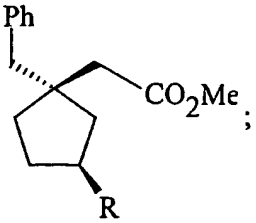
f) adding the product of Step e) to a mixture of iodomethane, a solvent, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and stirring to produce the

ester of formula (27)  ; or adding the product of Step e)

to methanol and an acid to produce the ester of formula (27)

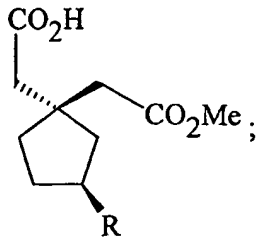
 ; or adding the product of Step e) to a solution of

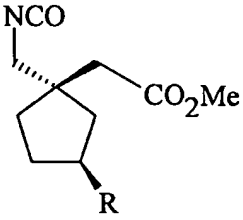
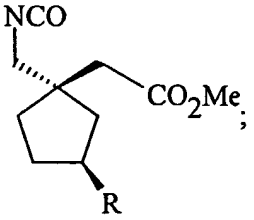
diazomethane or trimethylsilyl-diazomethane in a solvent to produce ester

of formula (27)  ;

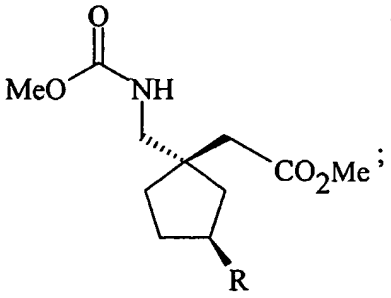
g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III)

chloride, and stirring to produce the carboxylic acid of formula (28)

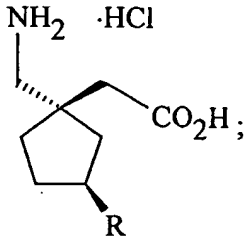


h) adding the product of Step g) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the isocyanate of formula (29)  ; or adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (29)  ;

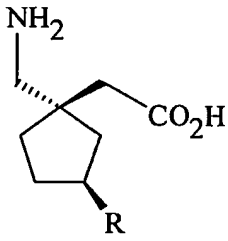
i) adding the product of Step h) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (30)



j) adding the product of Step i) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (IIIa)



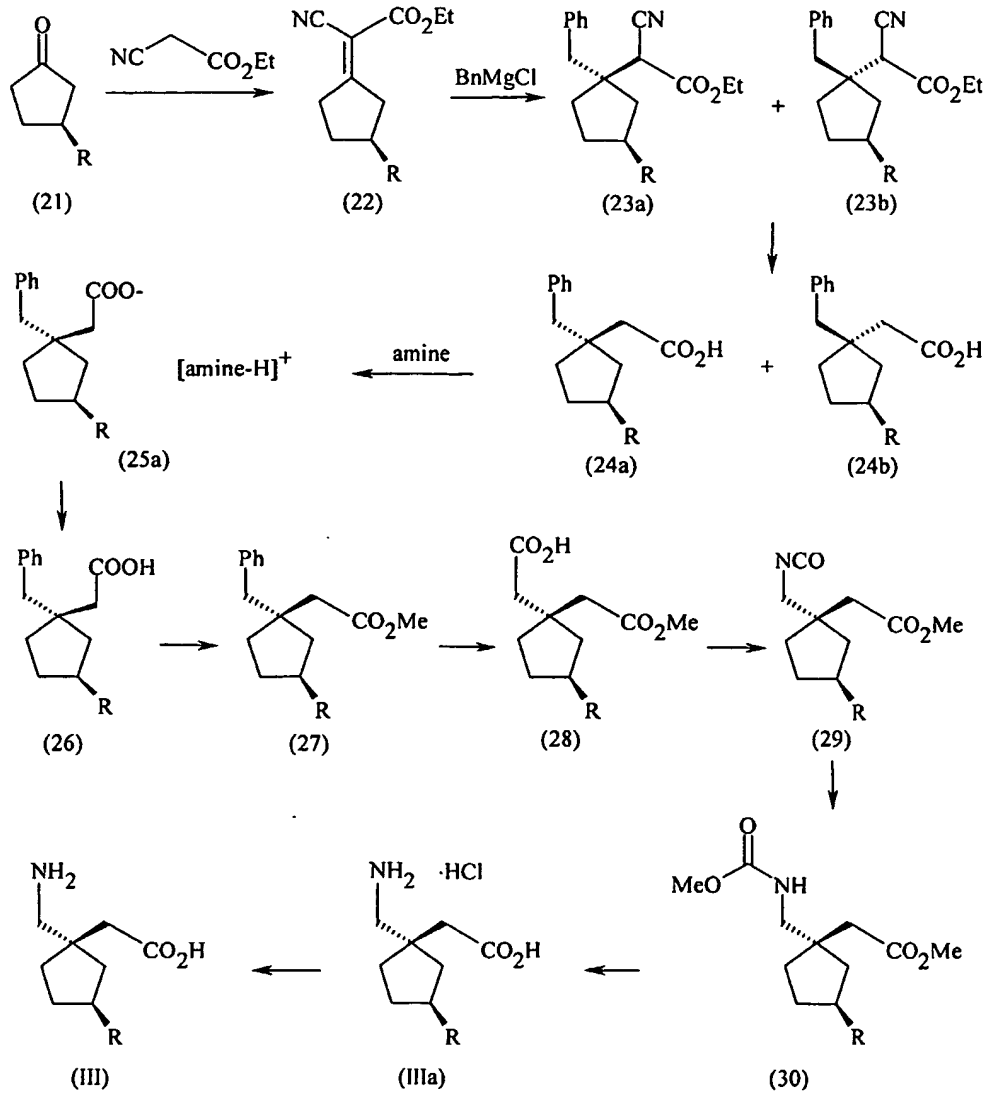
k) converting the product of Step j) to a compound of formula (III)



, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

This process is outlined in Scheme 4.

Scheme 4



Preferred is a process for the preparation of a compound of Formula III wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which acetic acid and β-alanine or ammonium acetate were added, and stirring the mixture at a temperature from 0°C to 150°C to produce the alkene of formula (22);

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in a dry solvent selected from tetrahydrofuran, 1,4-dioxane, *n*-heptane, toluene, ethyl ether, or *tert*-butyl methyl ether at a temperature from -100°C to 110°C to produce the addition products of formulas (23a) and (23b);

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, or cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, or diethylene glycol and stirring the mixture at a temperature from 25°C to 250°C to produce the carboxylic acids of formulas (24a) and (24b);

d) contacting the products of Step c) above with (R)-α-methyl-benzylamine in a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, or 1,4-dioxane at a temperature from -40°C to 105°C, and recrystallizing the salt so formed from a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, 1,4-dioxane, *tert*-butyl methyl ether, toluene, or *n*-heptane to produce the enriched diastereomer of formula (25a) as the (R)-α-methyl-benzylamine salt;

e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid to which water was added and stirring at a temperature from -40°C to 115°C to produce the carboxylic acid of formula (26);

f) adding the product of Step e) to a mixture of iodomethane in a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene, or 1,4-dioxane to which 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added, and stirring at a temperature from -40°C to 110°C to produce the ester of formula (27);

g) adding the product of Step f) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (28);

h) adding the product of Step g) to a mixture of a base selected from triethylamine or diisopropylethylamine and a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which diphenylphosphoryl azide (DPPA) was added, and stirring at a temperature from 0°C to 150°C to produce the isocyanate of formula (29);

i) adding the product of Step h) to a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which methanol was added and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (30);

j) adding the product of Step i) to a solvent selected from water, acetic acid, or 1,4-dioxane to which aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M was added, and stirring at a temperature from 0°C to 115°C to produce a compound of Formula IIIa;

k) converting the product of Step j) to a compound of Formula III, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

More preferred is a process for the preparation of a compound of Formula III wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in toluene to which acetic acid and ammonium acetate were added, and heating the mixture at reflux to produce the alkene of formula (22);

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to -20°C to produce the addition products of formulas (23a) and (23b);

c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C to produce the hydrolysis products of formulas (24a) and (24b);

d) contacting the products of Step c) above with (R)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (25a) as the (R)-α-methyl-benzylamine salt;

e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (26);

f) adding the product of Step e) to a mixture of iodomethane in dichloromethane to which 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added, and stirring to produce the ester of formula (27);

g) adding the product of Step f) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring to produce the carboxylic acid of formula (28);

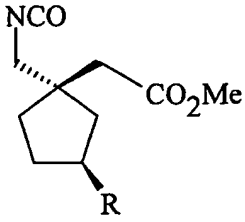
h) adding the product of Step g) to a mixture of triethylamine and toluene to which diphenylphosphoryl azide (DPPA) was added, and refluxing to produce the isocyanate of formula (29);

i) adding the product of Step h) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (30);

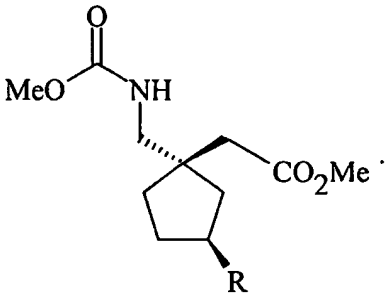
j) adding the product of Step i) to 1,4-dioxane to which aqueous hydrochloric acid at a concentration of 6 M was added, and stirring to produce a compound of Formula IIIa;

k) converting the product of Step j) to a compound of Formula III, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

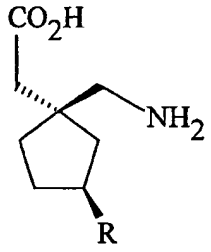
Also preferred is a process for the preparation of a compound of Formula III, further characterized in that the intermediate product (29)



formed is further reacted, without isolation, with methanol to produce the carbamate of formula (30)

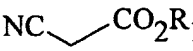


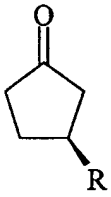
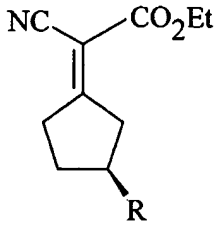
Further, the invention provides a process for the preparation of a compound of Formula IV



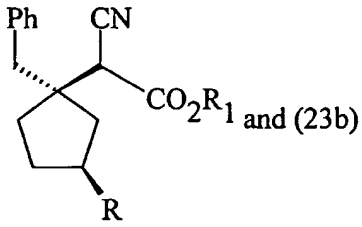
IV

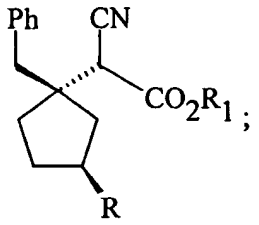
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)

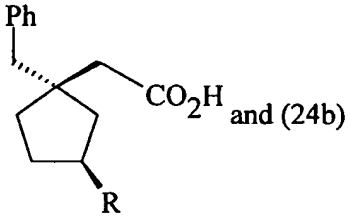
 , a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (22)  ;

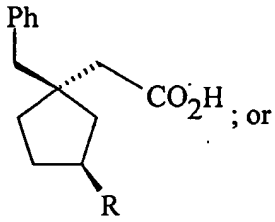
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition

of products of formulas (23a)  and (23b)

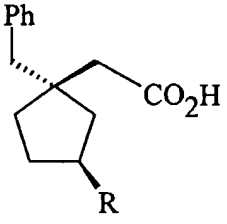
 ;

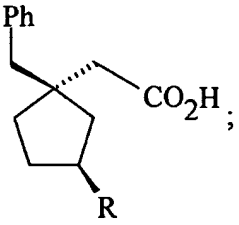
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying to produce the

carboxylic acids of formulas (24a)  and (24b)

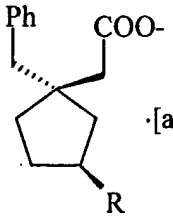
 ; or

adding the products of Step b) above to an acid mixture, and stirring to

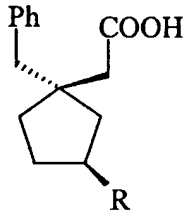
produce the carboxylic acids of formulas (24a) 

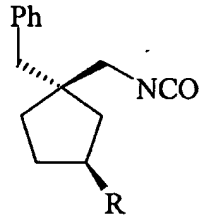
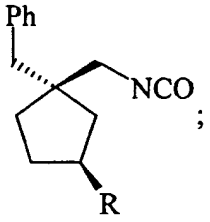
and (24b)  ;

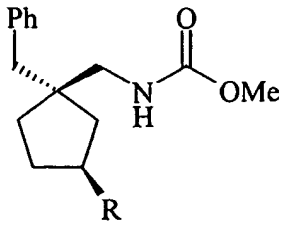
d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of

formula (25)  ·[amine-H]$^+$ as the amine salt; and

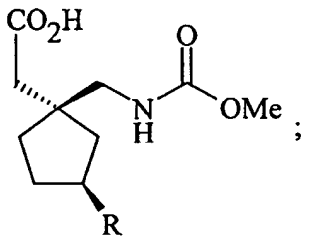
e) converting the product of Step d) to a carboxylic acid of formula (26)

 ;

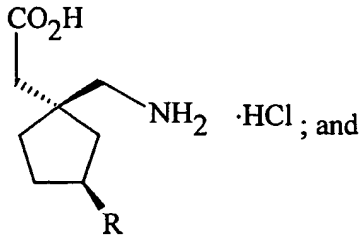
f) adding the product of Step e) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA) is added, and stirring to produce the isocyanate of formula (31)  ; or adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate of formula (31)  ;

g) adding the product of Step f) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (32)  ;

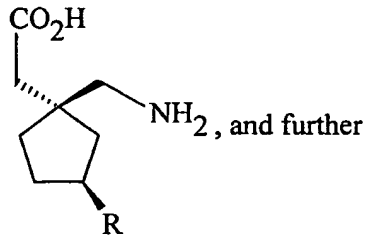
h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (33)

 ;

i) adding the product of Step h) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (IVa)

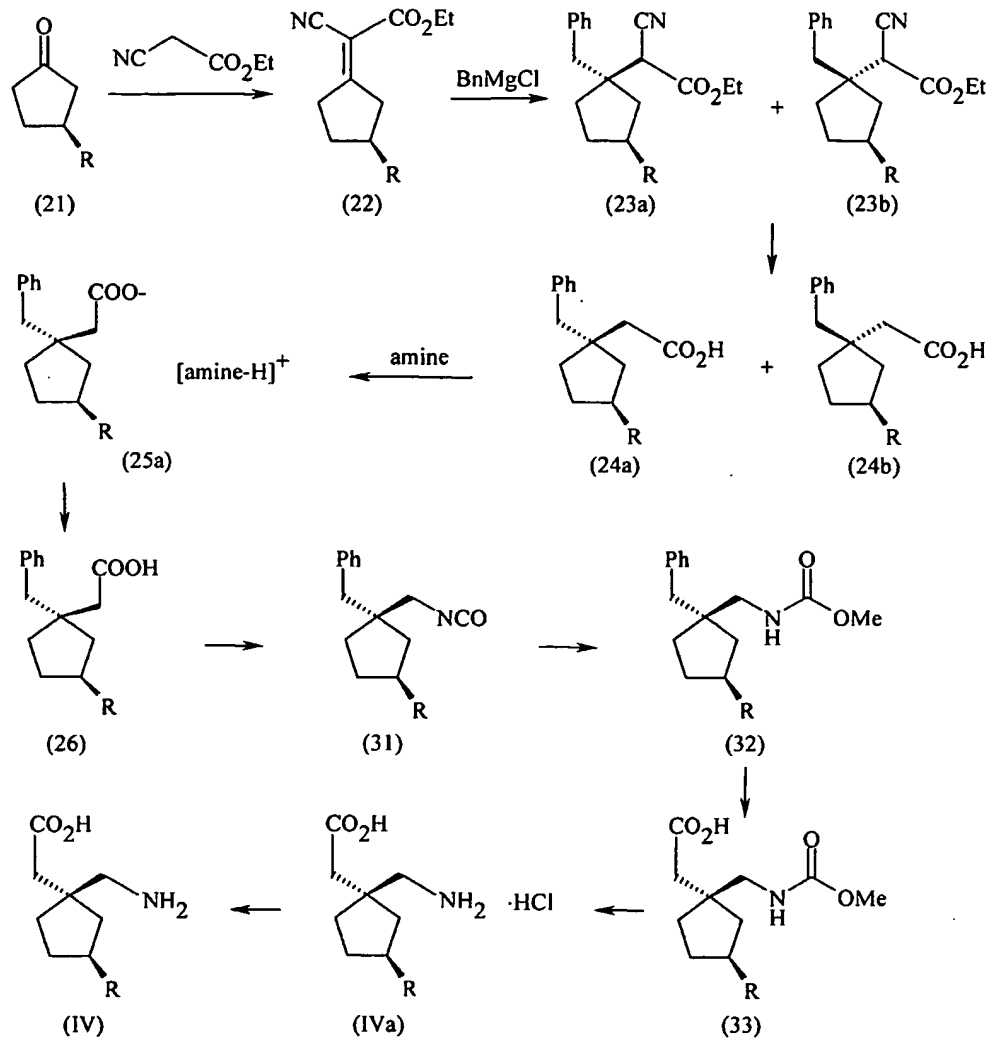
 ; and

j) converting the product of Step i) to a compound of formula (IV)

 , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

This process is outlined in Scheme 5.

Scheme 5



Preferred is a process for the preparation of a compound of Formula IV wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which acetic acid and β-alanine or ammonium acetate were added, and stirring the mixture at a temperature from 0°C to 150°C to produce the alkene of formula (22);

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in a dry solvent selected from tetrahydrofuran, 1,4-dioxane,

n-heptane, toluene, ethyl ether, or *tert*-butyl methyl ether at a temperature from -100°C to 110°C to produce the addition products of formulas (23a) and (23b);

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, or cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, or diethylene glycol and stirring the mixture at a temperature from 25°C to 250°C to produce the carboxylic acids of formulas (24a) and (24b);

d) contacting the products of Step c) above with (R)-α-methyl-benzylamine in a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, or 1,4-dioxane at a temperature from -40°C to 105°C, and recrystallizing the salt so formed from a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, 1,4-dioxane, *tert*-butyl methyl ether, toluene, or *n*-heptane to produce the enriched diastereomer of formula (25a) as the (R)-α-methyl-benzylamine salt;

e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid to which water was added and stirring at a temperature from -40°C to 115°C to produce the carboxylic acid of formula (26);

f) adding the product of Step e) to a mixture of a base selected from triethylamine or diisopropylethylamine and a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which diphenylphosphoryl azide (DPPA) was added, and stirring at a temperature from 0°C to 150°C to produce the isocyanate of formula (31);

g) adding the product of Step f) to a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which methanol was added and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (32);

h) adding the product of Step g) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride

were added, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (33);

i) adding the product of Step h) to a solvent selected from water, acetic acid, or 1,4-dioxane to which aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M was added, and stirring at a temperature from 0°C to 115°C to produce a compound of Formula IVa;

j) converting the product of Step i) to a compound of Formula IV, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

More preferred is a process for the preparation of a compound of Formula IV wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in toluene to which acetic acid and ammonium acetate were added, and heating the mixture at reflux to produce the alkene of formula (22);

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to -20°C to produce the addition products of formulas (23a) and (23b);

c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C to produce the hydrolysis products of formulas (24a) and (24b);

d) contacting the products of Step c) above with (R)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (25a) as the (R)-α-methyl-benzylamine salt;

e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (26);

f) adding the product of Step e) to a mixture of triethylamine and toluene to which diphenylphosphoryl azide (DPPA) was added, and refluxing to produce the isocyanate of formula (31);

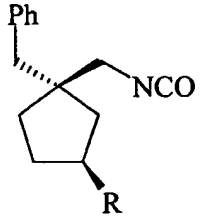
g) adding the product of Step f) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (32);

h) adding the product of Step g) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring to produce the carboxylic acid of formula (33);

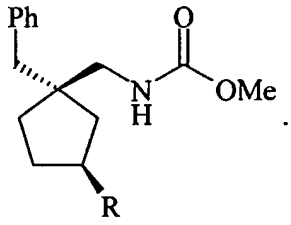
i) adding the product of Step h) to 1,4-dioxane to which aqueous hydrochloric acid at a concentration of 6 M was added, and stirring to produce a compound of Formula IVa;

j) converting the product of Step i) to a compound of Formula IV, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

Also preferred is a process for the preparation of a compound of Formula IV, further characterized in that the intermediate product (31)



formed is further reacted, without isolation, with methanol to produce the carbamate of formula (32)



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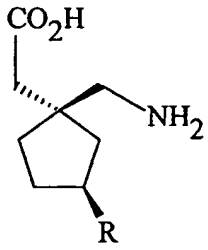
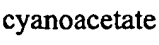
Still further, the invention provides a process for the preparation of a compound of Formula IV

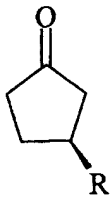


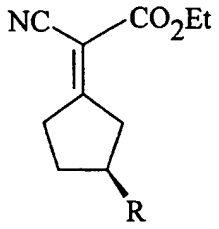
IV

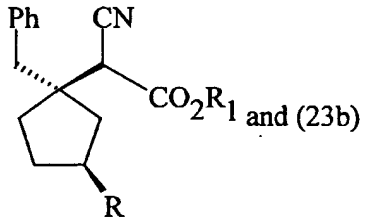
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

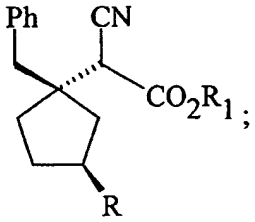
a) adding a cyanoacetate of formula (A) 

, wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)



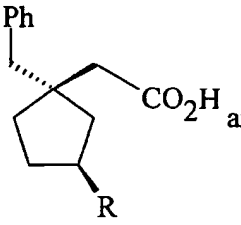
, a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (22)  ;

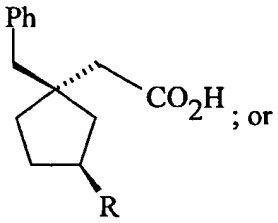
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition of products of formulas (23a)  and (23b)



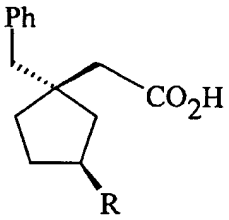
;

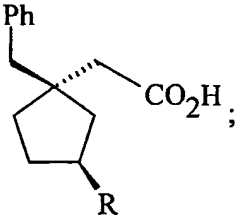
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying to produce the

carboxylic acids of formulas (24a)  and (24b)

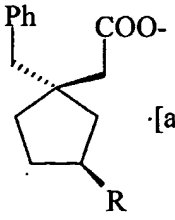
 ; or

adding the products of Step b) above to an acid mixture, and stirring to

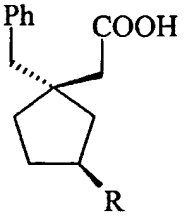
produce the carboxylic acids of formulas (24a) 

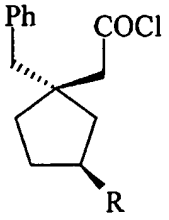
and (24b)  ;

d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of

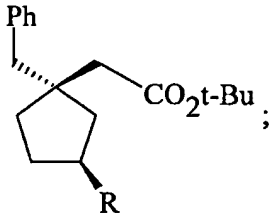
formula (25)  ·[amine-H]$^+$ as the amine salt; and

e) converting the product of Step d) to a carboxylic acid of formula (26)

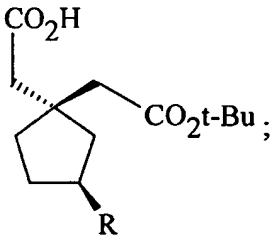
 ;

f) adding oxalyl chloride to a mixture of the product of Step e), a solvent, and N,N-dimethylformamide (DMF), and stirring to produce the acid chloride of formula (34) 

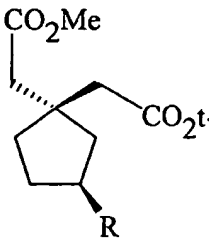
;

g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent, and a tertiary amine base, and stirring to produce the ester of formula (35) 

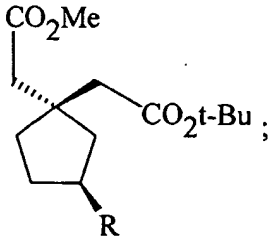
;

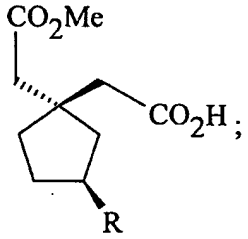
h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (36) 

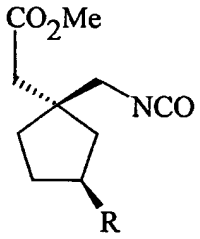
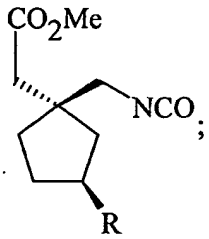
;

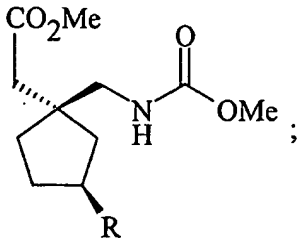
i) adding the product of Step h) to a mixture of a solvent, methanol, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of formula (37) 

; or adding the product of Step h) to a

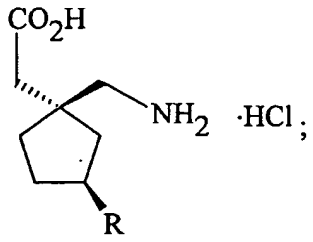
mixture of iodomethane, a solvent, and a base, and stirring to produce the bis ester of formula (37)  ;

j) adding an acid to a mixture of the product from Step i) and a solvent and stirring to produce the carboxylic acid of formula (38)  ;

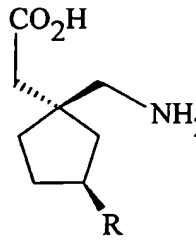
k) adding the product of Step j) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the isocyanate of formula (39)  ; or adding the product of Step j) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (39)  ;

l) adding the product of Step k) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (40)  ;

m) adding the product of Step l) to a mixture of a solvent and hydrochloric acid, and stirring to produce a compound of formula (IVa)

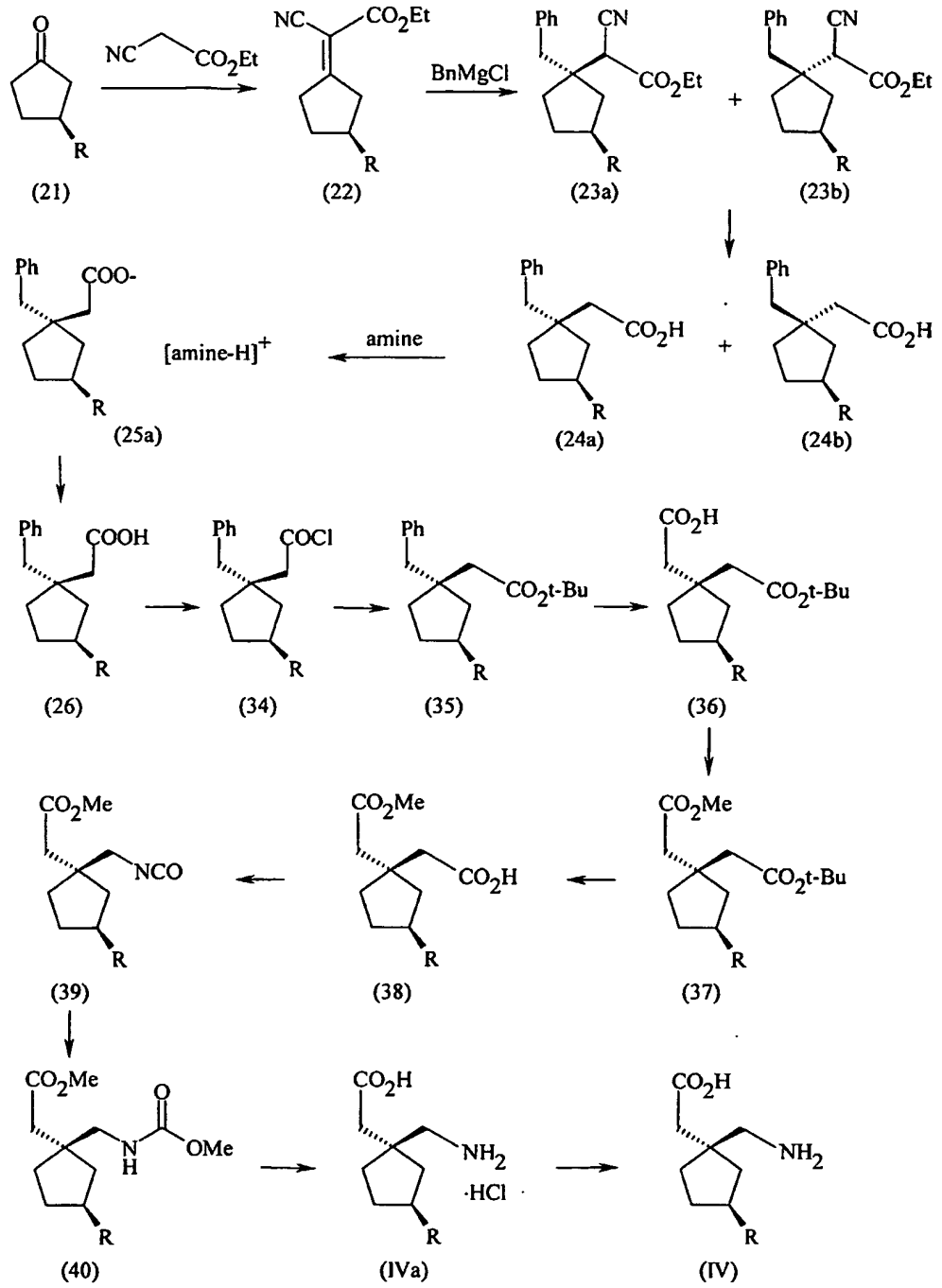
 ;

n) converting the product of Step m) to a compound of Formula IV

 , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

This process is outlined in Scheme 6.

Scheme 6



Preferred is a process for the preparation of a compound of Formula IV wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which acetic acid and β-alanine or ammonium acetate were added, and stirring the mixture at a temperature from 0°C to 150°C to produce the alkene of formula (22);

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in a dry solvent selected from tetrahydrofuran, 1,4-dioxane, *n*-heptane, toluene, ethyl ether, or *tert*-butyl methyl ether at a temperature from -100°C to 110°C to produce the addition products of formulas (23a) and (23b);

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, or cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, or diethylene glycol and stirring the mixture at a temperature from 25°C to 250°C to produce the carboxylic acids of formulas (24a) and (24b);

d) contacting the products of Step c) above with (R)-α-methyl-benzylamine in a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, or 1,4-dioxane at a temperature from -40°C to 105°C, and recrystallizing the salt so formed from a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, 1,4-dioxane, *tert*-butyl methyl ether, toluene, or *n*-heptane to produce the enriched diastereomer of formula (25a) as the (R)-α-methyl-benzylamine salt;

e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid to which water was added and stirring at a temperature from -40°C to 115°C to produce the carboxylic acid of formula (26);

f) adding oxalyl chloride to a mixture of the product of Step e) and a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, or *tert*-butyl methyl ether to which 0.01 mol percent to 10 mol percent of N,N-

dimethylformamide (DMF) was added, and stirring at a temperature from -40°C to 110°C to produce the acid chloride of formula (34);

g) adding the product of Step f) to a mixture of *tert*-butyl alcohol in a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, or *tert*-butyl methyl ether to which *N,N*-diisopropylethylamine (DIPEA) or triethylamine was added, and stirring at a temperature from -40°C to 110°C to produce the ester of formula (35);

h) adding the product of Step g) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (36);

i) adding the product of Step h) to a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which methanol and (trimethylsilyl)diazomethane were added, and stirring at a temperature from 0°C to 150°C to produce the bis ester of formula (37);

j) adding trifluoroacetic acid (TFA) to a mixture of the product from Step i) and a solvent selected from dichloromethane, chloroform, 1,4-dioxane, tetrahydrofuran, ethyl ether, or *tert*-butyl methyl ether and stirring at a temperature from -40°C to 110°C to produce the carboxylic acid of formula (38);

k) adding the product of Step j) to a mixture of a base selected from triethylamine or diisopropylethylamine and a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which diphenylphosphoryl azide (DPPA) was added, and stirring at a temperature from 0°C to 150°C to produce the isocyanate of formula (39);

l) adding the product of Step k) to a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which methanol was added and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (40);

m) adding the product of Step l) to a solvent selected from water, acetic acid, or 1,4-dioxane to which aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M was added, and stirring at a temperature from 0°C to 115°C to produce a compound of Formula IVa;

n) converting the product of Step m) to a compound of Formula IV, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

More preferred is a process for the preparation of a compound of Formula IV wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in toluene to which acetic acid and ammonium acetate were added, and heating the mixture at reflux to produce the alkene of formula (22);

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to -20°C to produce the addition products of formulas (23a) and (23b);

c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C to produce the hydrolysis products of formulas (24a) and (24b);

d) contacting the products of Step c) above with (R)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (25a) as the (R)-α-methyl-benzylamine salt;

e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (26);

f) adding oxalyl chloride to a mixture of the product of Step e) and dichloromethane to which a catalytic amount of N,N-dimethylformamide (DMF) was added, and stirring to produce the acid chloride of formula (34);

g) adding the product of Step f) to a mixture of *tert*-butyl alcohol in dichloromethane to which *N,N*-diisopropylethylamine (DIPEA) was added, and stirring to produce the ester of formula (35);

h) adding the product of Step g) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring to produce the carboxylic acid of formula (36);

i) adding the product of Step h) to a mixture of methanol and toluene to which (trimethylsilyl)diazomethane was added, and stirring to produce the bis ester of formula (37);

j) adding trifluoroacetic acid (TFA) to a mixture of the product from Step i) and dichloromethane, and stirring to produce the carboxylic acid of formula (38);

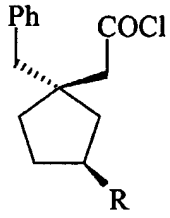
k) adding the product of Step j) to a mixture of triethylamine and toluene to which diphenylphosphoryl azide (DPPA) was added, and refluxing to produce the isocyanate of formula (39);

l) adding the product of Step k) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (40);

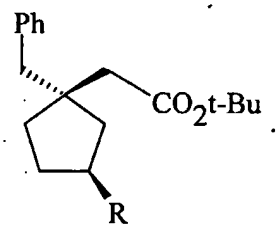
m) adding the product of Step l) to 1,4-dioxane to which aqueous hydrochloric acid at a concentration of 6 M was added, and stirring to produce a compound of Formula IVa;

n) converting the product of Step m) to a compound of Formula IV, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

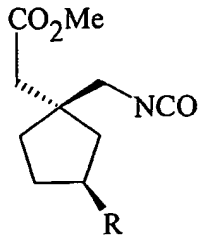
Also preferred is a process for the preparation of a compound of Formula IV, further characterized in that the intermediate product (34)

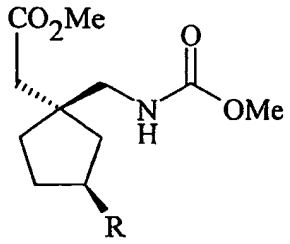


formed is further reacted, without isolation, with *tert*-butyl alcohol to produce the ester of formula (35)

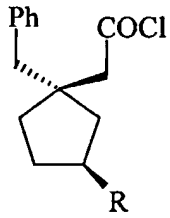


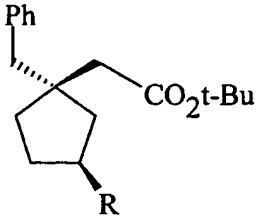
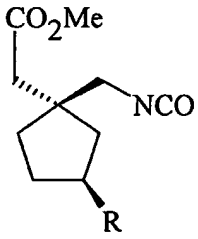
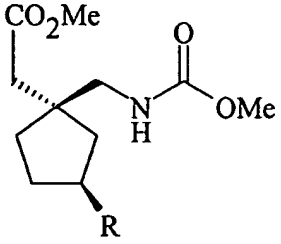
Also preferred is a process for the preparation of a compound of Formula IV, further characterized in that the intermediate product (39)



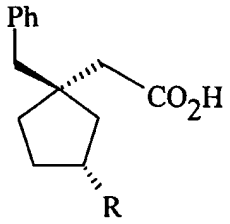
formed is further reacted, without isolation, with methanol to produce the carbamate of formula (40)  .

Also preferred is a process for the preparation of a compound of Formula IV, further characterized in that the intermediate product (34)



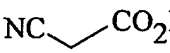
formed is further reacted, without isolation, with *tert*-butyl alcohol to produce the ester of formula (35)  and the intermediate product (39)  formed is further reacted, without isolation, with methanol to produce the carbamate of formula (40)  .

Further, the invention provides a process for the preparation of a compound of formula (6)

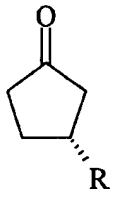


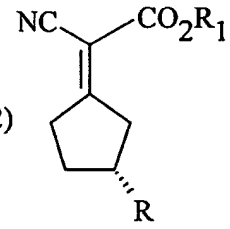
(6)

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A) 

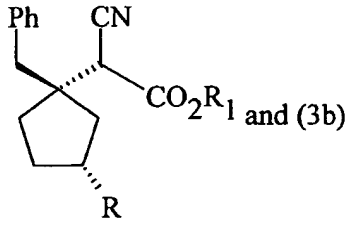
, wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (1)

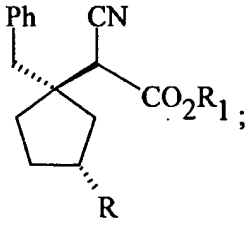


, a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (2) 

;

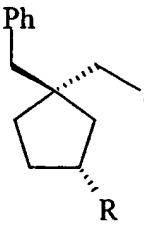
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition products of formulas (3a)

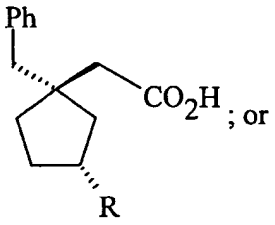


and (3b)


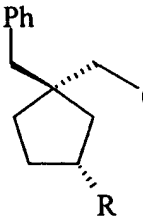
;

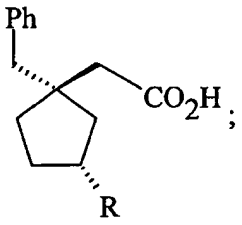
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, and a solvent, and stirring, and then acidifying to produce the

carboxylic acids of formulas (4a)  and (4b)

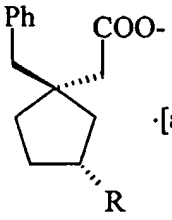


adding the products of Step b) above to an acid mixture and stirring to

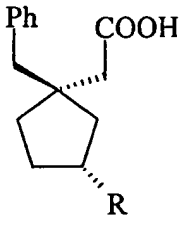
produce the carboxylic acids of formulas (4a)  and (4b)



d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of

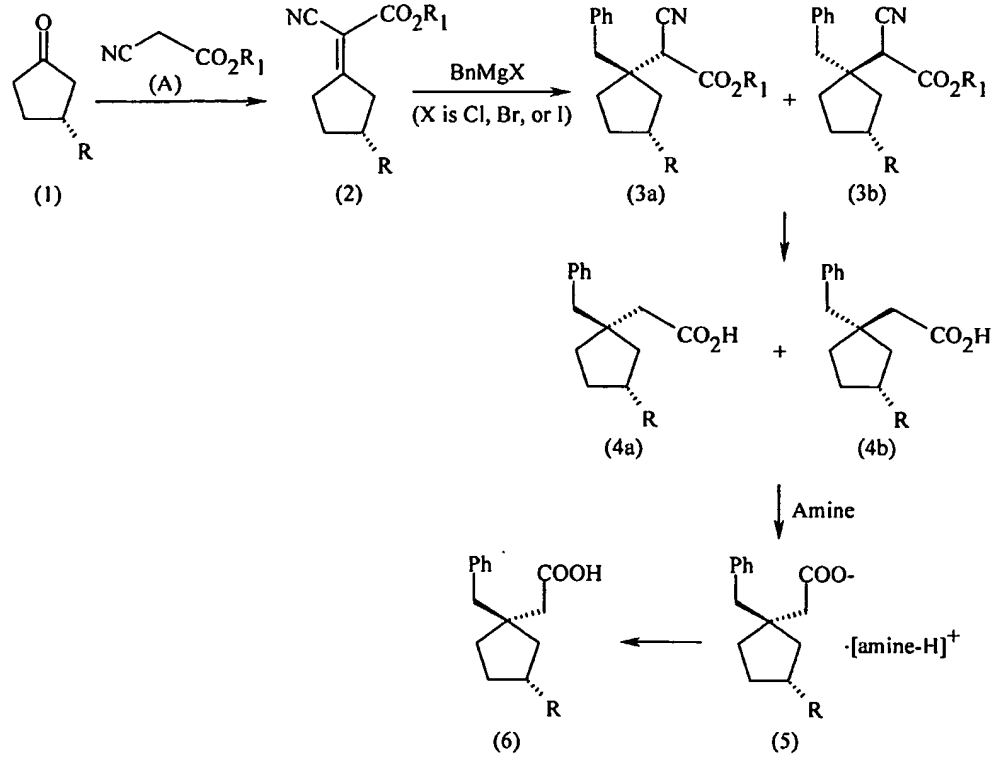
formula (5)  ·[amine-H]$^+$ as the amine salt; and

e) converting the product of Step d) to a carboxylic acid of formula (6)

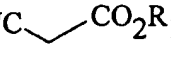
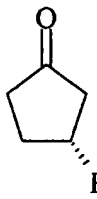


This process is outlined in Scheme 7.

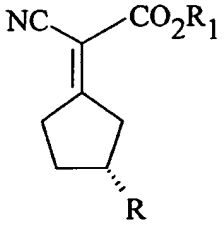
Scheme 7



Preferred is a process for the preparation of a compound of formula (6) wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

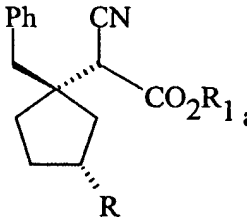
a) adding a cyanoacetate of formula (A)  wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of formula (1)  , a solvent selected from tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and

n-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

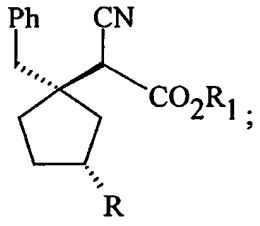


;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce the addition products of formulas (3a)

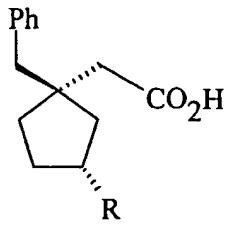


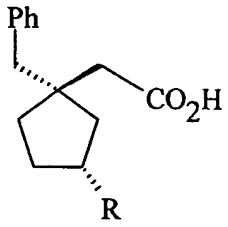
and (3b)

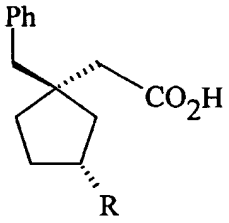


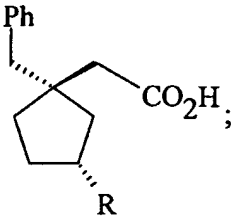
;

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture, and then acidifying to produce the carboxylic acids of formulas (4a)

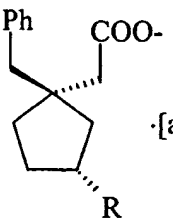


and (4b)


; or adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H_2SO_4, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of formulas (4a)


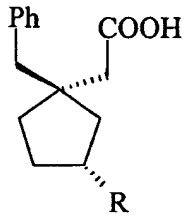
and (4b)


;

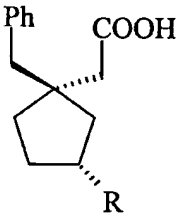
d) contacting the products of Step c) above with an amine selected from (S)-α-methyl-benzylamine, (R)-α-methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (5)


·[amine-H]$^+$ as the amine salt; and

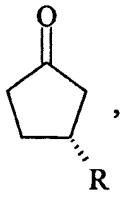
e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid dissolved in acetic acid and water, and stirring to produce the carboxylic acid of formula (6)



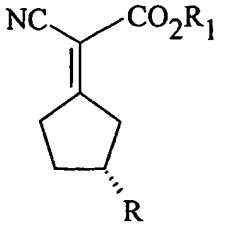
; or

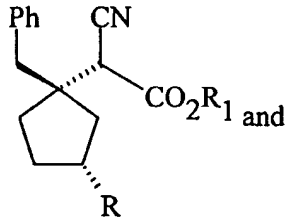
partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of formula (6)  .

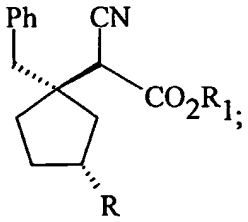
More preferred is a process for the preparation of a compound of formula (6) wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A) , wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)  ,

toluene, acetic acid, and a Knoevenagel reaction catalyst which is

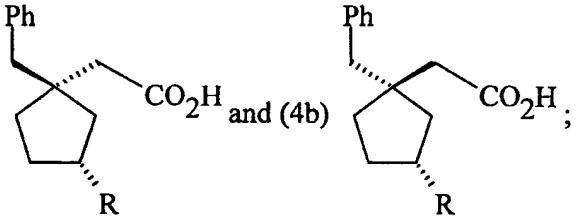
ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)  ;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition products of formulas (3a)  and



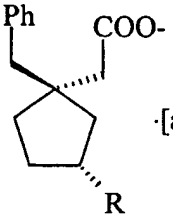
(3b) ;

c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of formulas (4a)

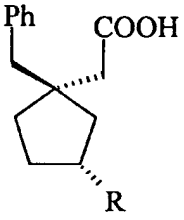


and (4b) ;

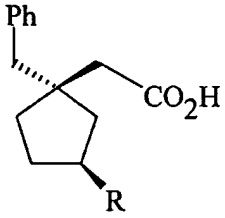
d) contacting the products of Step c) above with (S)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to

produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$

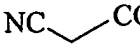
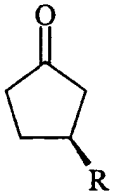
as the (S)-α-methyl-benzylamine salt;

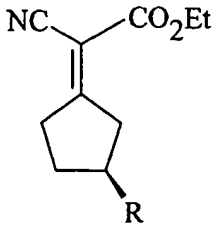
e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (6)  .

Further, the invention provides a process for the preparation of a compound of formula (26)

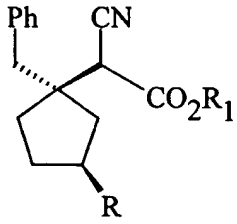
 (26)

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

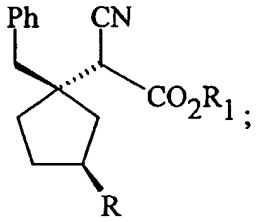
a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)  , a solvent, a carboxylic acid, and a Knoevenagel reaction

catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (22) 

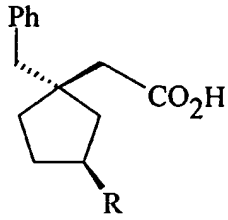
;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition of products of formulas (23a) 

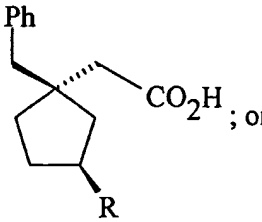
and (23b)



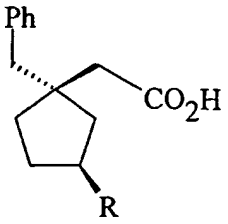
;

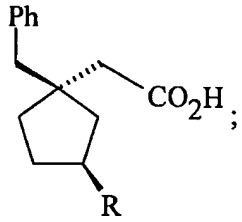
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, and a solvent, and stirring, and then acidifying to produce the carboxylic acids of formulas (24a) 

and (24b)

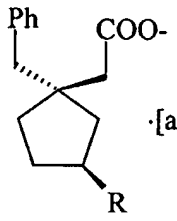


; or

adding the products of Step b) above to an acid mixture, and stirring to produce the carboxylic acids of formulas (24a) 

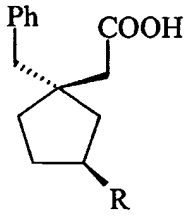
and (24b) 

;

d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (25) 

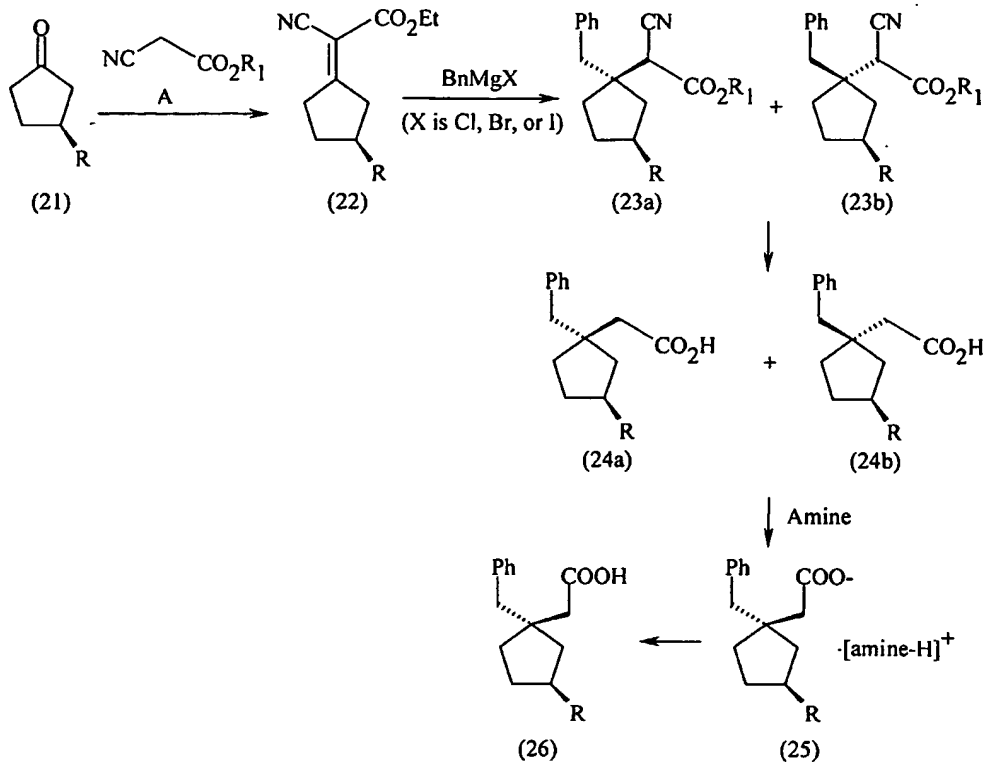
·[amine-H]$^+$ as the amine salt; and

e) converting the product of Step d) to a carboxylic acid of formula (26)

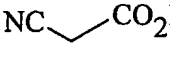
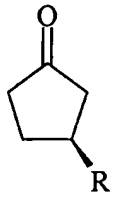


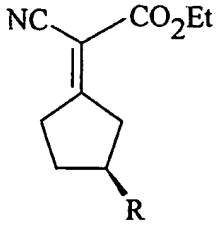
This process is outlined in Scheme 8.

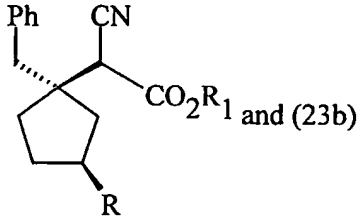
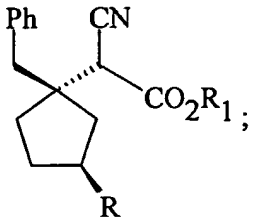
Scheme 8

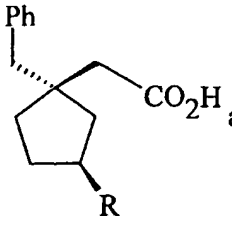
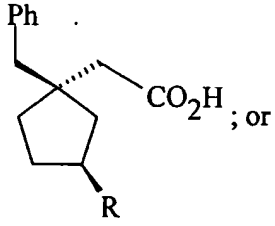


Preferred is a process for the preparation of a compound of formula (26) wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

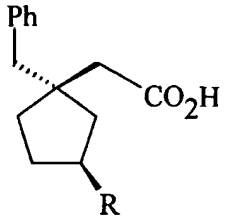
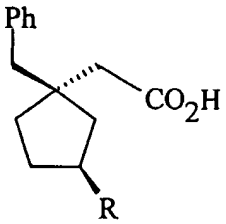
a) adding a cyanoacetate of formula (A)  , wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl, to a mixture of a chiral cyclopentanone of formula (21)  , a solvent selected from tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from

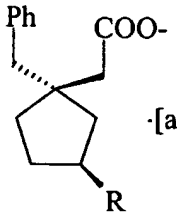
β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (22)  ;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce the addition products of formulas (23a)  and (23b)  ;

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture, and then acidifying to produce the carboxylic acids of formulas (24a)  and (24b)  ; or

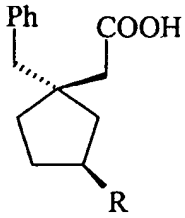
adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H_2SO_4, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of

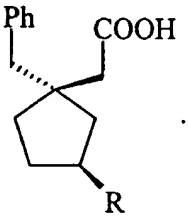
formulas (24a)  and (24b)  ;

d) contacting the products of Step c) above with an amine selected from (S)-α-methyl-benzylamine, (R)-α-methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (25)  ·[amine-H]$^+$ as the amine salt;

and

e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid dissolved in acetic acid and water, and stirring to produce the carboxylic acid of formula (26)

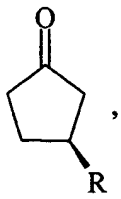
 ; or

partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of formula (26) 

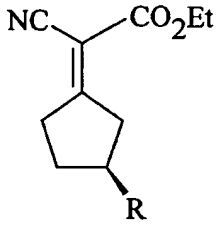
.

More preferred is a process for the preparation of a compound of formula (26) wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A)

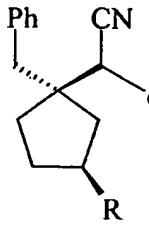
, wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (21) 

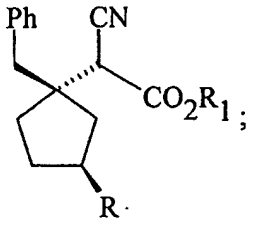
,

toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (22) 

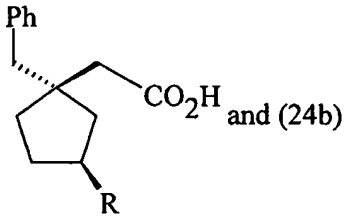
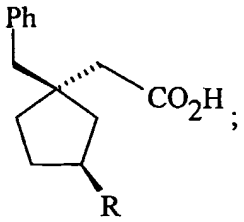
;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to -20°C to produce the addition

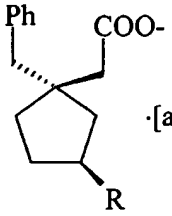
products of formulas (23a)  and (23b)

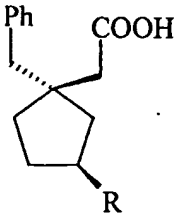
 ;

c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of formulas (24a)

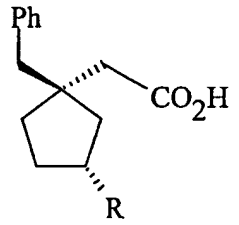
 and (24b)  ;

d) contacting the products of Step c) above with (R)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (25)

 ·[amine-H]$^+$ as the (R)-α-methyl-benzylamine salt; and

e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (26)  .

Further, the invention provides a key intermediate of formula (6)



(6)

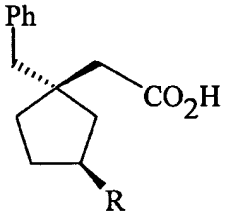
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof.

Preferred is a compound of formula (6) and pharmaceutically acceptable salts thereof wherein R is C_1-C_{10} alkyl.

More preferred is a compound of formula (6) and pharmaceutically acceptable salts thereof wherein R is selected from methyl, ethyl, and n-propyl.

Still more preferred is a compound of formula (6) named ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid.

Further, the invention provides a key intermediate of formula (26)



(26)

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof.

Preferred is a compound of formula (26) and pharmaceutically acceptable salts thereof wherein R is C_1-C_{10} alkyl.

More preferred is a compound of formula (26) and pharmaceutically acceptable salts thereof wherein R is selected from methyl, ethyl, and n-propyl.

Still more preferred is a compound of formula (26) named ((1R,3S)-1-benzyl-3-methyl-cyclopentyl)-acetic acid.

Further, the invention provides a compound of Formula I, wherein R is as defined above, prepared according to any one of the processes for the preparation of a compound of Formula I described above.

Preferred is a compound of Formula I, wherein R is C_1-C_{10} alkyl, prepared according to any one of the processes for the preparation of a compound of Formula I described above.

More preferred is a compound of Formula I, wherein R is selected from methyl, ethyl, and *n*-propyl, prepared according to any one of the processes for the preparation of a compound of Formula I described above.

Still more preferred is a compound of Formula I selected from:

((1R,3S)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid; and

((1R,3S)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride, prepared according to any one of the processes for the preparation of a compound of Formula I described above.

Further, the invention provides a compound of Formula II, wherein R is as defined above, prepared according to any one of the processes for the preparation of a compound of Formula II described above.

Preferred is a compound of Formula II, wherein R is C_1-C_{10} alkyl, prepared according to any one of the processes for the preparation of a compound of Formula II described above.

More preferred is a compound of Formula II, wherein R is selected from methyl, ethyl, and *n*-propyl, prepared according to any one of the processes for the preparation of a compound of Formula II described above.

Still more preferred is a compound of Formula II selected from:

((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid; and

((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride, prepared according to any one of the processes for the preparation of a compound of Formula II described above.

Further, the invention provides a compound of Formula III, wherein R is as defined above, prepared according to any one of the processes for the preparation of a compound of Formula III described above.

Further, the invention provides a compound of Formula IV, wherein R is as defined above, prepared according to any one of the processes for the preparation of a compound of Formula IV described above.

Further, the invention provides a compound of formula (6), wherein R is as defined above, prepared according to any one of the processes for the preparation of a compound of formula (6) described above.

Preferred is a compound of formula (6), wherein R is C_1-C_{10} alkyl, prepared according to any one of the processes for the preparation of a compound of formula (6) described above.

More preferred is a compound of formula (6), wherein R is selected from methyl, ethyl, and *n*-propyl, prepared according to any one of the processes for the preparation of a compound of formula (6) described above.

Still more preferred is a compound of formula (6) named ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid, prepared according to any one of the processes for the preparation of a compound of formula (6) described above.

Further, the invention provides a compound of formula (26), wherein R is as defined above, prepared according to any one of the processes for the preparation of a compound of formula (26) described above.

Preferred is a compound of formula (26), wherein R is C_1-C_{10} alkyl, prepared according to any one of the processes for the preparation of a compound of formula (26) described above.

More preferred is a compound of formula (26), wherein R is selected from methyl, ethyl, and *n*-propyl, prepared according to any one of the processes for the preparation of a compound of formula (26) described above.

Still more preferred is a compound of formula (26) named ((1R,3S)-1-benzyl-3-methyl-cyclopentyl)-acetic acid, prepared according to any one of the processes for the preparation of a compound of formula (26) described above.

Further, the invention provides a compound of Formula I selected from:

((1R,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid;

((1R,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

((1R,3R)-1-aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

((1R,3R)-1-aminomethyl-3-ethyl-cyclopentyl)-acetic acid hydrochloride;

((1R,3R)-1-aminomethyl-3-propyl-cyclopentyl)-acetic acid; and

((1R,3R)-1-aminomethyl-3-propyl-cyclopentyl)-acetic acid hydrochloride.

Further, the invention provides a compound of Formula II selected from:

((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid;

((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

((1S,3R)-1-aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

((1S,3R)-1-aminomethyl-3-ethyl-cyclopentyl)-acetic acid hydrochloride;

((1S,3R)-1-aminomethyl-3-propyl-cyclopentyl)-acetic acid; and

((1S,3R)-1-aminomethyl-3-propyl-cyclopentyl)-acetic acid hydrochloride.

Further, the invention provides compounds selected from:

E-Cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester;

Z-Cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester;

(R)-((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester;

(S)-((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester;

(R)-((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester;

(S)-((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester;

((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentylmethyl)-benzene;

((1S,3R)-1-Benzyl-3-methyl-cyclopentylmethyl)-carbamic acid methyl ester;

[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid;

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid methyl ester;

(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid;

((1R,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester;

[(1R,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester;

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid *tert*-butyl ester;

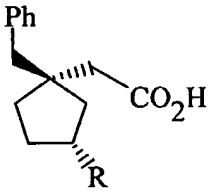
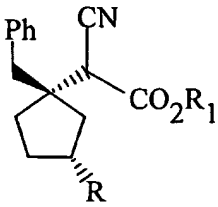
[(1S,3R)-1-Carboxymethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester;

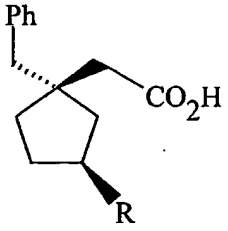
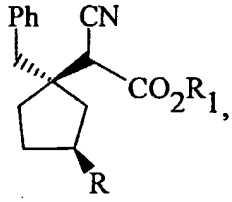
[(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester;

((1R,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid;

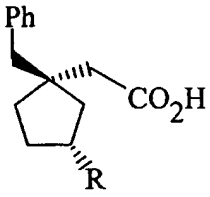
((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester; and

[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester.

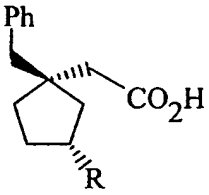
More preferred is a process for the preparation of a compound of formula (4a)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, comprising, hydrolyzing a compound of formula (3a)  , wherein R_1 is H, alkyl, or benzyl.

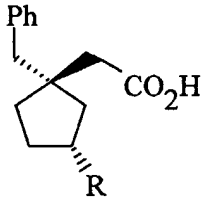
More preferred is a process for the preparation of a compound of formula (24a)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, comprising, hydrolyzing a compound of formula (23a)  , wherein R_1 is H, alkyl, or benzyl.

More preferred is a process for the preparation of a compound of

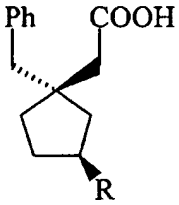
formula (6)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl,

comprising, resolving a

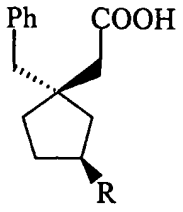
mixture containing compounds of formulas (4a)  and (4b)

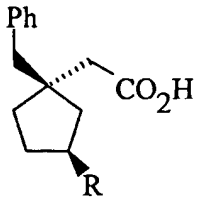
 wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl.

More preferred is a process for the preparation of a compound of

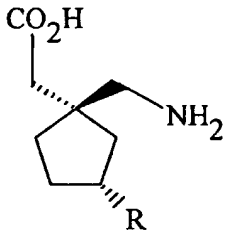
formula (26)  wherein R is C1-C_{10} alkyl or C_3-C_{10} cycloalkyl,

comprising, resolving a

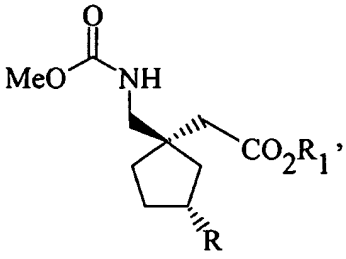
mixture containing compounds of formulas (24a)  and

(24b)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl.

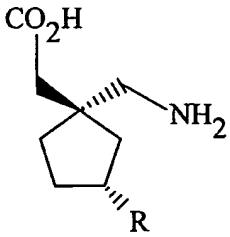
More preferred is a process for the preparation of a compound of

Formula I  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl,

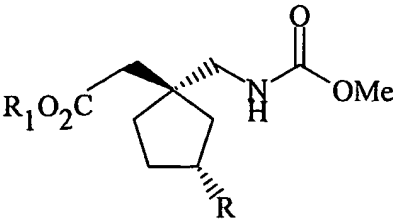
and pharmaceutically acceptable salt thereof, comprising, hydrolyzing a

compound of formula (41)  , wherein R_1 is H, alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

More preferred is a process for the preparation of a compound of

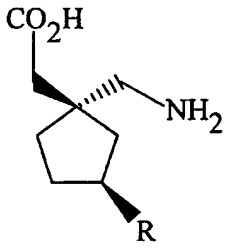
Formula II  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl,

and pharmaceutically acceptable salt thereof, comprising, hydrolyzing a

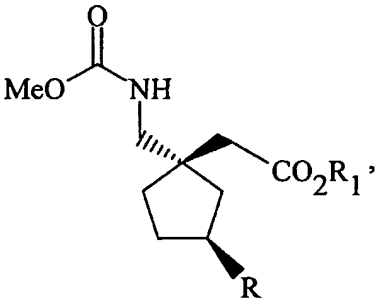
compound of formula (42)  , wherein R_1 is H,

alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

More preferred is a process for the preparation of a compound of

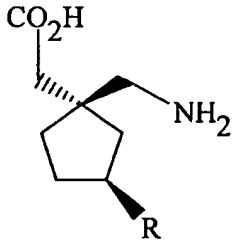
Formula III  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl,

and pharmaceutically acceptable salt thereof, comprising, hydrolyzing a

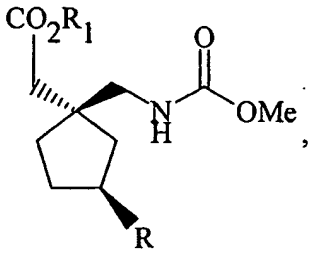
compound of formula (43)  , wherein R_1 is H, alkyl,

or benzyl, and contacting the product, if desired, with an acid or a base.

More preferred is a process for the preparation of a compound of

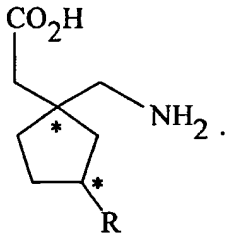
Formula IV  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl,

and pharmaceutically acceptable salt thereof, comprising, hydrolyzing a

compound of formula (44)  , wherein R_1 is H, alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

DETAILED DESCRIPTION OF THE INVENTION

The instant invention is an important process as it permits the synthesis of single isomers; it is a route to stereospecific 3-substituted 5-membered rings of formula

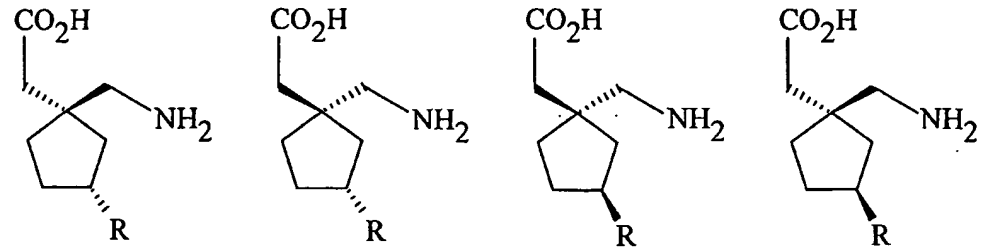


A key feature of the invention is the stereoselective preparation of a compound of formula (6) by selective fractional crystallization of a salt of formula (5) from a mixture of compounds of formulas (4a) and (4b), and conversion of a salt of formula (5) to a compound of formula (6). Another feature of the invention is the conversion of a compound of formula (2) to a mixture of compounds of formulas (3a) and (3b) wherein the yield of a compound of formula (3a) over a diastereomer of formula (3b) may be enhanced by optimizing certain reaction parameters such as, for example, temperature. Reaction of a compound of formula (2) at a relatively low temperature generally provides for a relatively higher yield of a compound of formula (3a) over (3b) than when the reaction is run at a higher temperature. The invention also provides for translation of the stereochemistry at the two chiral carbons of the cyclopentane ring of the resulting pure enantiomer of formula (6) into enantiomerically pure compounds of Formulas I or II with little or no racemization.

Another key feature of the invention is the stereoselective preparation of a compound of formula (26) by selective fractional crystallization of salt of formula (25) from a mixture of compounds of formulas (24a) and (24b), and conversion of a salt of formula (25) to a compound of formula (26). Another feature of the invention is the conversion of a compound of formula (22) to a mixture of compounds of formulas (23a) and (23b) wherein the yield of a compound of formula (23a) over a diastereomer of formula (23b) may be enhanced by optimizing certain reaction parameters such as, for example, temperature. Reaction of a compound of formula (22) at a relatively low temperature generally provides for a relatively higher yield of a compound of formula (23a) over (23b) than when the reaction is run at a higher temperature. The invention also provides for translation of the stereochemistry at the two chiral carbons of the cyclopentane ring of the resulting pure enantiomer of formula (26) into enantiomerically pure compounds of Formulas III or IV with little or no racemization.

The final products are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal disorders such as irritable bowel syndrome (IBS), inflammation especially arthritis, sleep disorders, premenstrual syndrome, and hot flashes.

The following experimental procedures provide a novel route to be used to stereoselectively synthesize 3-substituted cyclopentyl-based analogs of gabapentin and pharmaceutically acceptable salts thereof. These routes provide access to pure stereoisomers of Formulas I, II, III, and IV



I II III IV

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl.

Examples 1 and 3 below each show a synthesis of a compound of Formula II wherein R is methyl.

Example 2 below shows a synthesis of a compound of Formula I wherein R is methyl.

It is understood that compounds of Formulas I, II, III, or IV, or a pharmaceutically acceptable salt thereof, produced by a hydrolysis reaction such as, for example, step j) in the above process for the preparation of a compound of Formula I, or a pharmaceutically acceptable salt thereof, or the process described above wherein a compound of formula (41) is hydrolyzed, may be formed as an acid or base salt thereof, which salt may be optionally converted to a free amino acid form or a pharmaceutically acceptable salt form thereof by methods well known to a skilled person in the pharmaceutical or chemical arts.

The following terms are defined as used herein.

As used herein the term "C_1-C_{10} alkyl" means a straight or branched alkyl group or radical containing from 1 to 10 carbon atoms. Illustrative examples of C_1-C_{10} alkyl include methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-1-propyl, 1,1-dimethylethyl, 1-pentyl, 2-pentyl, 3-pentyl, 2,2-dimethylpropyl, 1-hexyl, 2-hexyl, 3-hexyl, 4-methyl-1-pentyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 5-methyl-1-hexyl, 1-octyl, 2-octyl, 3-octyl, 4-octyl, 6-methyl-1-heptyl, 5,5-dimethylhexyl, 1-nonyl, 2-nonyl, 1-decyl, and 2-decyl.

The term "C_3-C_{10} cycloalkyl" means a cycloalkyl group or radical having from 3 to 10 carbon atoms. Illustrative examples of a C_3-C_{10} cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl.

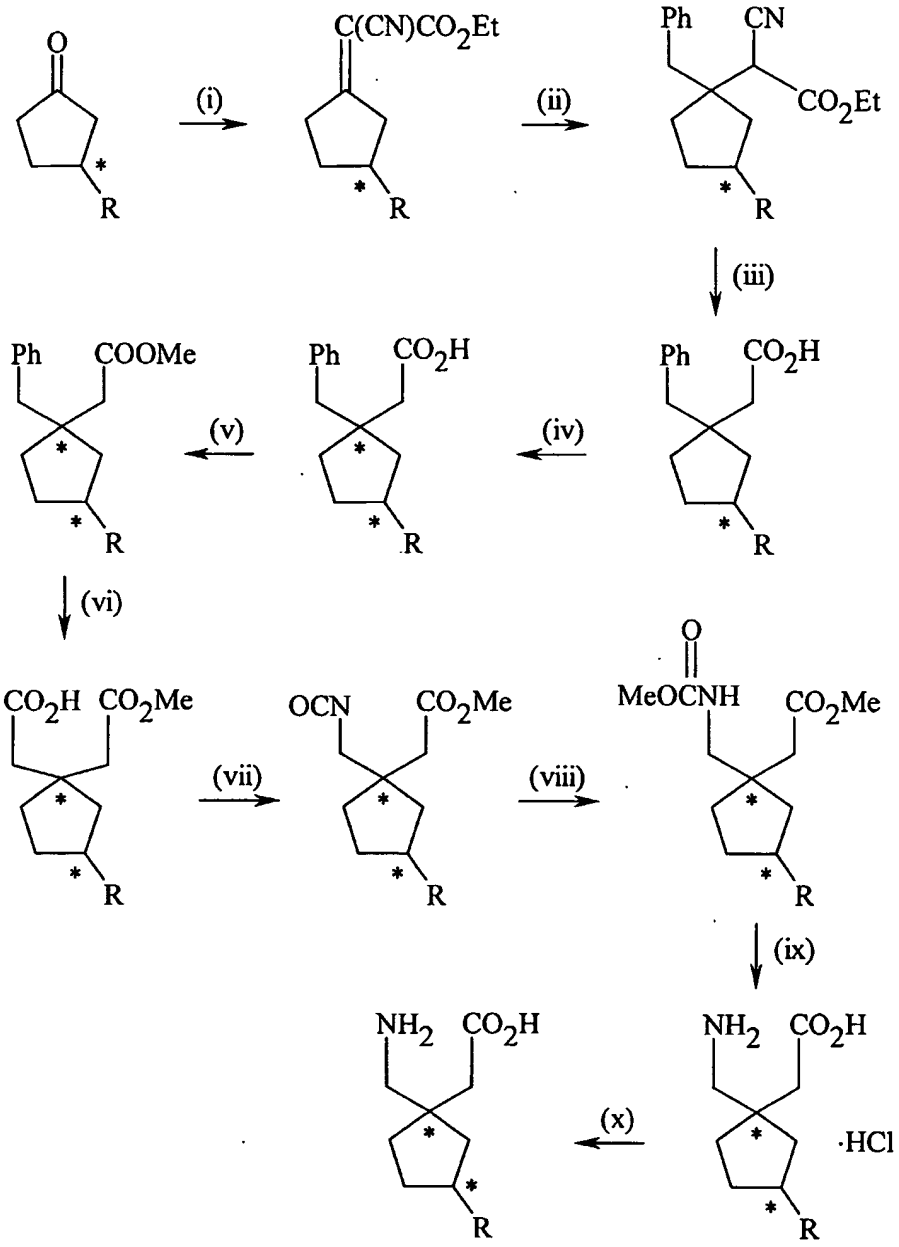
The term "stereoisomer" means any of a group of isomers in which identical atoms are linked in the same order but differ in their spatial arrangement.

*	Asterisk symbol points out an enantiomerically enriched chiral carbon atom
AcOH	Acetic acid
Alkali hydroxide	LiOH, NaOH, KOH, or CsOH

NH_4OAc	Ammonium acetate
BnMgCl or $PhCH_2MgCl$	Benzylmagnesium chloride
t-BuOH or *tert*-butyl alcohol	1,1-Dimethylethanol
^{t}Butyl	1,1-Dimethylethyl
CH_2Cl_2	Dichloromethane
CCl_4	Carbon tetrachloride
$CDCl_3$	Deuterochloroform
$(CH_3)_3SiCHN_2$	Trimethylsilyldiazomethane
CN	Carbon-nitrogen triple bond (nitrile)
$(COCl)_2$	Oxalyl chloride
CsOH	Cesium hydroxide
de	Diastereomeric excess
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterated dimethylsulfoxide
ee	Enantiomeric excess
Et	Ethyl
EtOAc	Ethyl acetate
Et_3N	Triethylamine
HCl	Hydrogen chloride
HCl (aq)	Hydrochloric acid
6*N* HCl	6 normal hydrochloric acid
HCl (g)	Hydrogen chloride (gaseous)
^{1}H-NMR	Proton (nuclear) magnetic resonance spectroscopy
IR	Infrared spectroscopy
J	Coupling constant in Hz
KOH	Potassium hydroxide
LCMS	Liquid chromatography-mass spectrometry
LiOH	Lithium hydroxide

Me	Methyl
MeO	Methoxy
MeCN	Acetonitrile
MeI	Iodomethane
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
MS (ES^+)	Positive ion electrospray mass spectrometry
MS (ES^-)	Negative ion electrospray mass spectrometry
MS (CI^+)	Positive ion chemical ionization mass spectrometry
MS (CI^-)	Negative ion chemical ionization mass spectrometry
m/z	mass per unit charge
$NCCH_2CO_2Et$	Ethyl cyanoacetate
$NaIO_4$	Sodium periodate
NaOH	Sodium hydroxide
ODS	Octadecyl-functionalized silica gel
Ph	Phenyl
$(i\text{-Pr})_2NEt$	Diisopropylethylamine
R_f	R_f value
$RuCl_3$	Ruthenium(III) chloride
$SOCl_2$	Thionyl chloride
TFA or CF_3CO_2H	Trifluoroacetic acid
THF	Tetrahydrofuran

General Route A



Reagents and Conditions:

(i) $NCCH_2CO_2Et$, catalyst (e.g., NH_4OAc, ACOH);

(ii) BnMgCl;

(iii) hydrolysis using, for example, alkali hydroxide (e.g., KOH);

(iv) a) resolution using a resolving agent (e.g., (R)- or (S)-α-methylbenzylamine);

b) conversion of the enriched stereoisomer to the free acid using, for example, hydrochloric acid;

(v) esterification using, for example, MeI and DBU;

(vi) oxidation using, for example, $RuCl_3$ and $NaIO_4$;

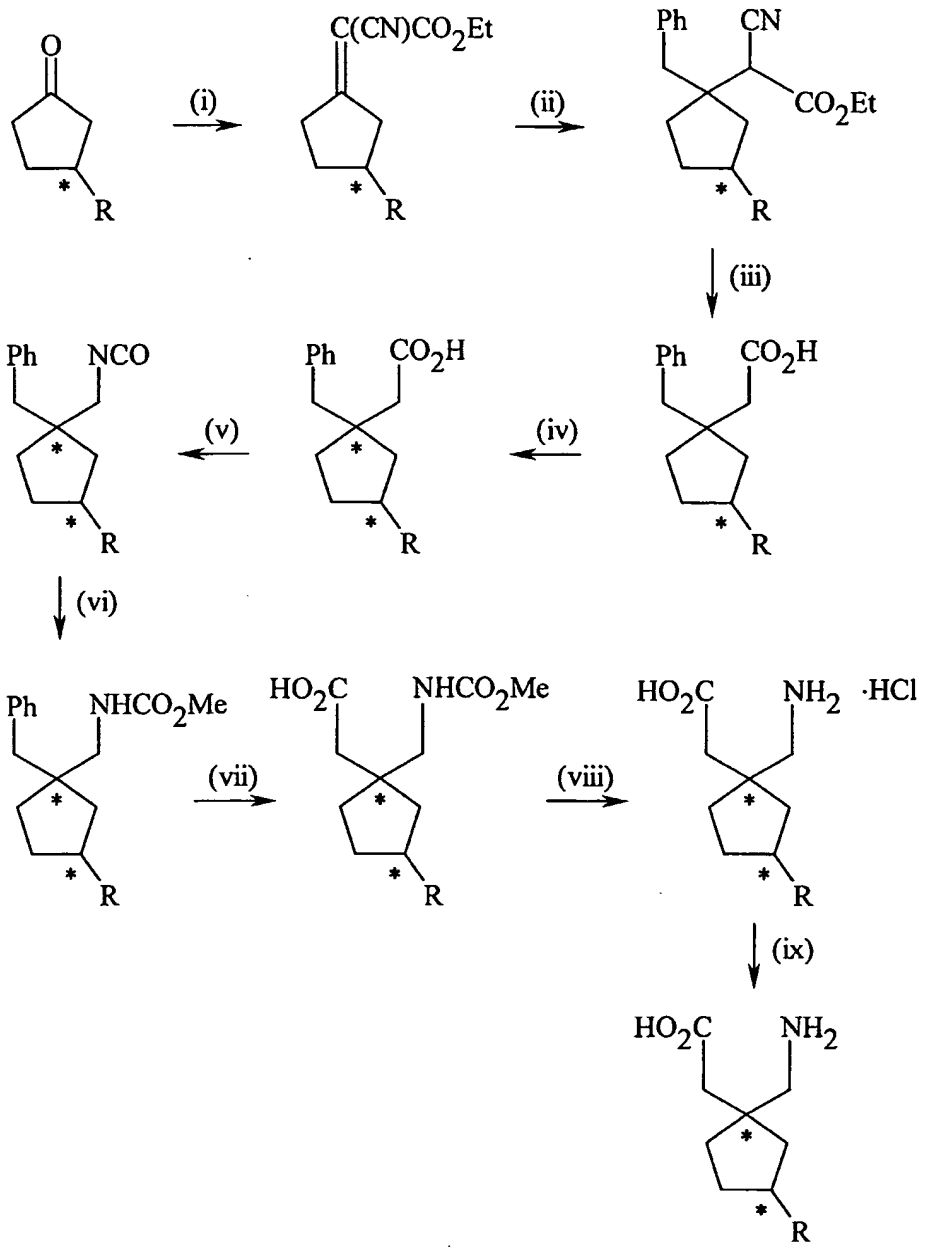
(vii) $(PhO)_2P(O)N_3$ and a base (e.g., Et_3N);

(viii) MeOH;

(ix) hydrolysis using HCl (aq);

(x) conversion to the free amino acid using, for example, H_2O and alkali hydroxide (e.g., NaOH).

General Route B



Reagents and Conditions:

(i) $NCCH_2CO_2Et$, catalyst (e.g., NH_4OAc, ACOH);

(ii) BnMgCl;

(iii) hydrolysis using, for example, alkali hydroxide (e.g., KOH);

(iv) a) resolution using a resolving agent (e.g., (R)- or (S)-α-methylbenzylamine);

b) conversion of salt of enriched stereoisomer to the free acid using, for example, hydrochloric acid;

(v) $(PhO)_2P(O)N_3$ and base (e.g., Et_3N);

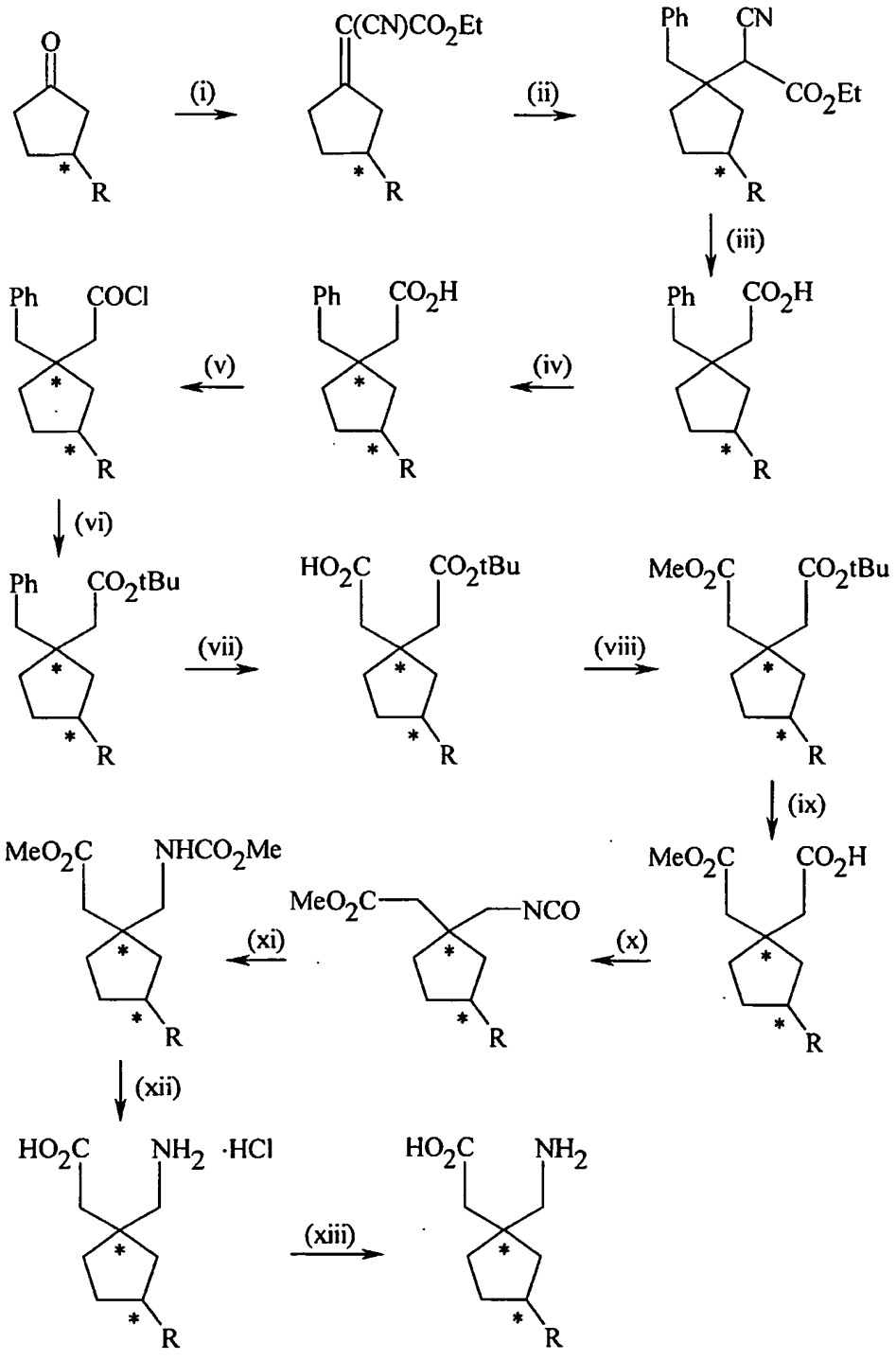
(vi) MeOH;

(vii) oxidation using, for example, $RuCl_3$ and $NaIO_4$;

(viii) hydrolysis using HCl (aq);

(ix) conversion to the free amino acid using, for example, H_2O and alkali hydroxide (e.g., NaOH).

General Route C



Reagents and Conditions:

(i) $NCCH_2CO_2Et$, catalyst (e.g., NH_4OAc, ACOH);

(ii) BnMgCl;

(iii) hydrolysis using, for example, alkali hydroxide (e.g., KOH);

(iv) a) resolution using a resolving agent (e.g., (R)- or (S)-α-methylbenzylamine);

b) conversion of salt of enriched stereoisomer to the free acid using, for example, hydrochloric acid;

(v) chlorination using, for example, $(COCl)_2$ or $SOCl_2$;

(vi) tBuOH and base (e.g., Et_3N);

(vii) oxidation using, for example, $RuCl_3$ and $NaIO_4$;

(viii) esterification using, for example, $(CH_3)_3SiCHN_2$ and MeOH;

(ix) dealkylation using, for example, CF_3CO_2H;

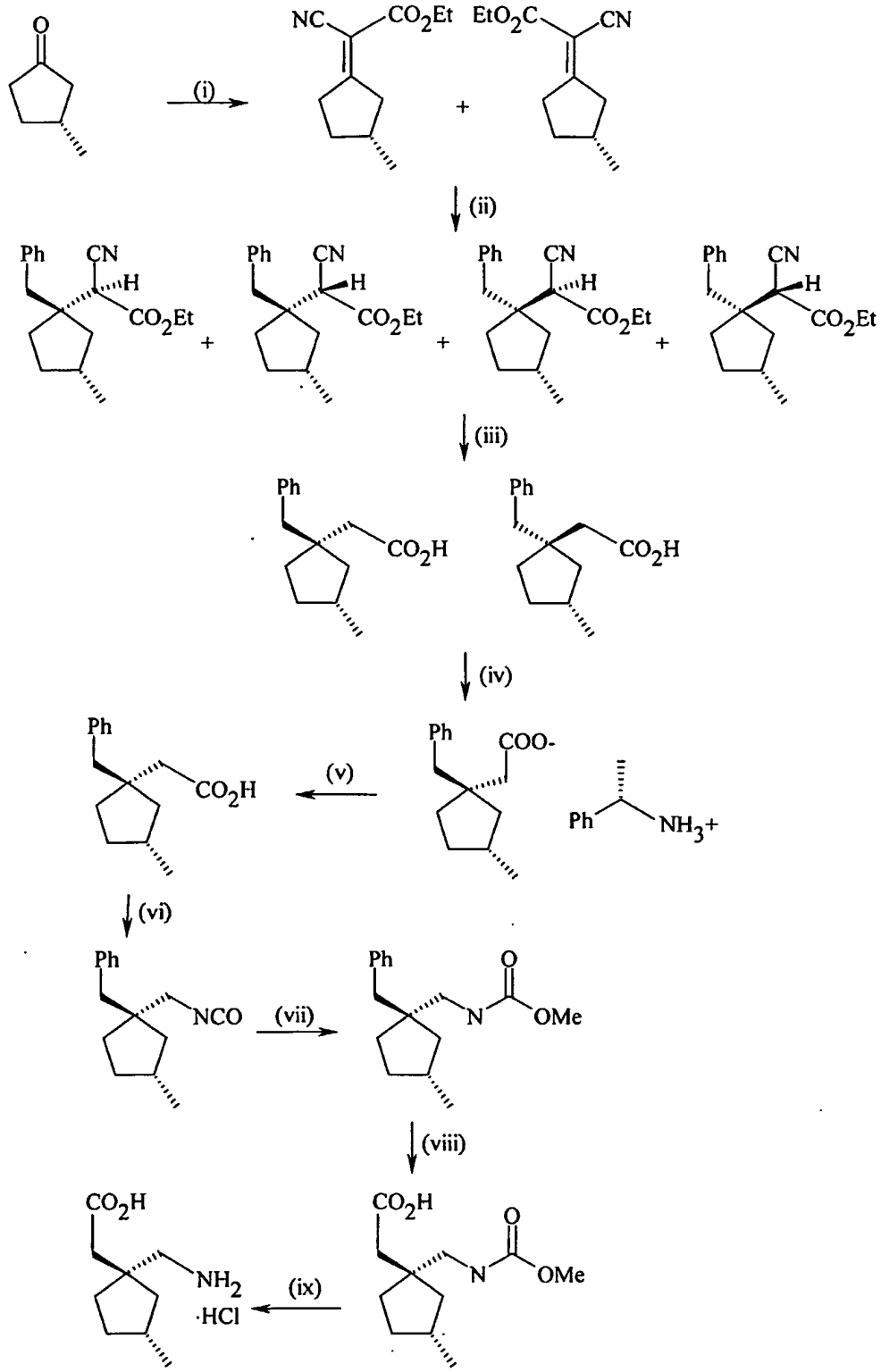
(x) $(PhO)_2P(O)N_3$ and a base (e.g., Et_3N);

(xi) MeOH;

(xii) hydrolysis using HCl (aq);

(xiii) conversion to the free amino acid using, for example, H_2O and alkali hydroxide (e.g., NaOH).

EXAMPLE 1


O
(i)
NC
CO2Et
EtO2C
CN
+
(ii)
Ph
CN
H
CO2Et
+
+
+
(iii)
Ph
CO2H
Ph
CO2H
(iv)
Ph
CO2H
(v)
Ph
COO-
Ph
NH3+
(vi)
Ph
NCO
(vii)
Ph
O
N
OMe
(viii)
CO2H
O
N
OMe
CO2H
NH2
·HCl
(ix)

(i) $NCCH_2CO_2Et$, NH_4OAc, AcOH, toluene, reflux;

(ii) $PhCH_2MgCl$, THF, -78°C;

(iii) KOH, ethylene glycol, 160°C;

(iv) (S)-(-)-α-methyl benzylamine, EtOAc, 0°C;

(v) HCl (aq);

(vi) $(PhO)_2P(O)N_3$, Et_3N, toluene, reflux;

(vii) MeOH, toluene, reflux;

(viii) $RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O;

(ix) *6N* HCl, 1,4-dioxane.

(E and Z)-Cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester

(R)-(+)-3-Methylcyclopentanone (5 g, 51.0 mmol), ethyl cyanoacetate (5.42 mL, 51.0 mmol), ammonium acetate (0.4 g, 5.1 mmol), and glacial acetic acid (0.58 mL, 10.2 mmol) were refluxed in toluene (30 mL) using a Dean-Stark trap. After 6 hours, the mixture was allowed to cool and diluted with ethyl acetate (100 mL), washed with water (3 × 80 mL), brine, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel, heptane/ethyl acetate, 9:1) to give 8.87 g (90%) of a 1:1 mixture of (E and Z)-cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester;

R_f (heptane-ethyl acetate, 9:1) 0.28;

IR thin film(cm^{-1}) 2225 (CN), 1724 (C=O), 1617 (C=C);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 4.27 (2H, q, *J* 7.2, CO_2CH_2Me), 4.26 (2H, q, *J* 7.2, CO_2CH_2Me), 3.35 (1H, dt, *J* 7.1, 1.6), 3.30 (1H, dt, *J* 7.1, 1.6), 3.23 (1H, ddd, *J* 8.1, 3.5, 1.7), 3.18 (1H, ddd, *J* 8.1, 3.4, 1.7), 3.05-2.67 (4H, m), 2.50-2.32 (2H, m), 2.29-1.96 (4H, m), 1.50-1.35 (2H, m), 1.34 (3H, t, *J* 7.2, CO_2CH_2Me), 1.33 (3H, t, *J* 7.1, CO_2CH_2Me), 1.10 (3H, d, *J* 6.6, Me), 1.08 (3H, d, *J* 6.6, Me);

MS (ES^-): *m/z* 192 (M-H, 100%).

(R and S)-((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester and (R and S)-((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester

A mixture of (E and Z)-cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester (4.13 g, 21.4 mmol) in THF (30 mL) was added over 1 hour to a stirring solution of benzylmagnesium chloride (27.7 mL of a 1 M solution in ether, 27.7 mmol) in THF (50 mL) at -78°C under argon. After stirring for a further 1 hour, the mixture was quenched by addition of saturated ammonium chloride solution (15 mL). The mixture was allowed to warm to room temperature, diluted with ether (30 mL), and dilute hydrochloric acid (20 mL) was added. The organic layer was separated, and the aqueous layer was further extracted with ether (2 × 40 mL). The combined ether layers were washed with brine, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel, heptane-ethyl acetate, 95:5) to give 5.8 g (100%) of a 7:7:3:3 mixture of diastereomeric (R and S)-((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester and (R and S)-((1R,3R)-1-benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester;

R_f (heptane-ethyl acetate, 9:1) 0.32;

IR thin film (cm^{-1}) 2246 (CN), 1740 (C=O), 1603 (C=C);

MS (ES^-) *m/z* 284 (M-H, 100%).

<u>((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid and ((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid</u>

The mixture of (R and S)-((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester and (R and S)-((1R,3R)-1-benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester (1 g, 3.5 mmol) and potassium hydroxide (1.2 g, 21.4 mmol) were heated to 160°C in ethylene glycol (5 mL) for 16 hours. After this time, the mixture was allowed to cool and dilute hydrochloric acid (150 mL) was added carefully. The mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic fractions were washed with brine, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel, heptane/ethyl acetate, 98:2) to give 0.65 g (80%) of a 7:3 mixture of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid and ((1R,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid as an oil;

R_f (heptane-ethyl acetate, 98:2) 0.36;

IR thin film (cm^{-1}) 1702 (C=O);

^{1}H-NMR (400 MHz; $CDCl_3$) major isomer ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid: δ 7.31-7.21 (5H, m, Ph), 2.82 (1H, d, *J* 13.4, $CH_AH_BCO_2H$), 2.76 (1H, d, *J* 13.4, $CH_AH_BCO_2H$), 2.33 (2H, br s, CH_2Ph), 2.19-1.66 (m), 1.62-1.52 (m), 1.11 (1H, dd, *J* 13.0, 9.9), 1.01 (3H, d, *J* 6.6, Me); minor isomer ((1R,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid: δ 7.31-7.21 (5H, m, Ph), 2.89 (1H, d, *J* 13.2, $CH_AH_BCO_2H$), 2.84 (1H, d, *J* 13.4, $CH_AH_BCO_2H$), 2.28 (2H, br s, CH_2Ph), 2.19-1.66 (m), 1.62-1.52 (m), 1.30-1.17 (m), 1.00 (3H, d, *J* 6.6, Me);

MS (CI^-): *m/z* 231 (M-H, 100%).

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid

(s)-(-)-α-Methyl benzylamine (8.8 g, 72.7 mmol) was added to a stirring solution of the diastereomeric mixture of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid and ((1R,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid (16.9 g, 72.7 mmol) dissolved in the minimum quantity of ethyl acetate. The mixture was placed in the fridge and left for 1 hour. After this time, the acid salt had crystallised out and this was filtered off. The salt was recrystallized several times from ethyl acetate (to 95% de). The salt was taken up in ethyl acetate, washed with dilute hydrochloric acid, brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give 6.8 g (40%) of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid; LCMS (Prodigy® (Phenomenex, Ltd.) ODS 3 50 mm × 4.6 mm id column, 5-50% Acetonitrile/water) Retention Time = 2.01 min, 98% purity.

((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentylmethyl)-benzene

Diphenylphosphoryl azide (4.48 g, 16 mmol), triethylamine (1.69 g, 16.8 mmol), and acid ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid (3.74 g, 16 mmol) were refluxed in toluene (40 mL) for 17 hours. The mixture was allowed to cool

and then taken up in ethyl acetate (150 mL), washed with saturated aqueous sodium hydrogen carbonate (200 mL), brine (150 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 3.69 g (100%) of ((1S,3R)-1-isocyanatomethyl-3-methyl-cyclopentylmethyl)-benzene, which was used without further purification;

R_f (heptane-ethyl acetate, 8:2) 0.36;

IR thin film (cm^{-1}) 2262 (CN).

((1S,3R)-1-Benzyl-3-methyl-cyclopentylmethyl)-carbamic acid methyl ester

((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentylmethyl)-benzene (3.69 g, 16 mmol) was refluxed in methanol (10 mL) and toluene (20 mL) for 16 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, heptane-ethyl acetate 9:1) to give 2.66 g (63%) of ((1S,3R)-1-benzyl-3-methyl-cyclopentylmethyl)-carbamic acid methyl ester;

R_f (heptane-ethyl acetate, 8:2) 0.28;

IR thin film (cm^{-1}) 1709 (C=O);

^{1}H-NMR (400 MHz; $CDCl_3$) δ 7.32-7.16 (5H, m, Ph), 4.60 (1H, bs, *NH*), 3.68 (3H, s, OMe), 3.18-3.00 (2H, m, CH_2NH), 2.62-2.60 (2H, s, CH_2Ph), 0.99 (3H, d, *J* 6.8, Me), 2.05-1.92, 1.87-1.72, 1.60-1.40, 1.00-0.89 (7H, m);

MS (ES^+) *m/z* 262 (M+H, 90%), 302 (M+CH_3CN+H,100%);

LCMS (Prodigy® ODS 3 50 mm × 4.6 mm id column, 5-50% Acetonitrile (0.05% formic acid)/water (0.05% formic acid)) Retention Time = 2.11, 94% de.

[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid

((1S,3R)-1-Benzyl-3-methyl-cyclopentylmethyl)-carbamic acid methyl ester (2.6 g, 9.9 mmol) and sodium periodate (29.8 g, 140 mmol) were stirred together in carbon tetrachloride (30 mL), acetonitrile (30 mL), and water for 6 hours. The mixture was cooled to 0°C, and ruthenium(III) chloride (0.04 g, 0.2 mmol) was added to the reaction mixture. The reaction was allowed to warm to room

temperature and stirred for 20 hours. Diethyl ether (50 mL) was added, and the mixture was then extracted with saturated aqueous sodium hydrogen carbonate (200 mL). The aqueous layer was acidified to pH 1 with 4N hydrochloric acid and re-extracted with ethyl acetate (200 mL), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was purified by chromatography (silica gel, eluting with a gradient of heptane to 1:1 heptane:ethyl acetate) to give 0.32 g (14%) of [(1S,3R)-1-(methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid;

R_f (heptane-ethyl acetate, 8:2) 0.30;

IR thin film (cm^{-1}) 3338 (NH), 1712 (C=O);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 9.29 (1H, s, COOH), 5.17 (1H, bs, NH), 3.71 (3H, s, OMe), 3.30 (1H, dd, *J* 14.4, 7.1, $CH_AH_BNH_2$), 3.17 (1H, dd, *J* 14.4, 6.6, $CH_AH_BNH_2$), 2.37 (2H, s, CH_2COOH), 2.20-1.00 (7H, m), 1.01 (3H, d, *J* 6.4, CH*Me*);

MS (ES^+) *m/z* 230 (M+H, 63%), 481 (M+Na,100).

((1S,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride

[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid (0.32 g, 1.4 mmol) was refluxed in a mixture of 1,4-dioxane (3 mL) and 6N Hydrochloric acid (8 mL) for 4 hours. The mixture was allowed to cool, diluted with water (200 mL), and washed with dichloromethane (2 × 200 mL). The aqueous layer was evaporated under reduced pressure, and the residue was recrystallized from ethyl acetate/methanol to give 0.17 g (59%) of ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

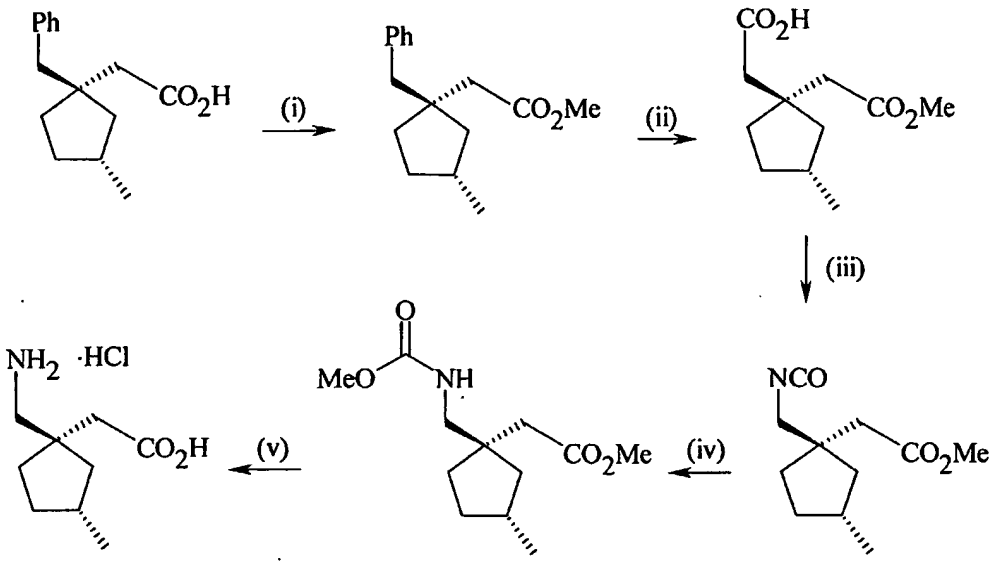
IR thin film (cm^{-1}) 1710 (C=O);

^{1}H-NMR (400 MHz; DMSO-d_6): δ 2.96 (1H, d, *J* 12.8, $CH_AH_BNH_2$), 2.90 (1H, d, *J* 12.8, $CH_AH_BNH_2$), 2.40 (2H, s, CH_2COOH), 2.04 (1H, m, C*H*Me), 1.81-1.61, 1.51-1.43, 1.21-1.11 (5H, m), 1.06 (1H, dd, *J* 12.8, 10.4), 0.97 (3H, d, *J* 6.35, Me);

MS (ES^+) *m/z* 173 (M+H, 100%), 196 (M+Na, 10%);

LCMS (Prodigy® ODS 3 50 mm x 4.6 mm id column, 5% for 2 min, 5-50% over 1.5 min of Acetonitrile (0.05% formic acid)/water (0.05% formic acid)) Retention Time = 0.92, 94% de.

EXAMPLE 2



(i) $(CH_3)_3SiCHN_2$, MeOH, toluene;

(ii) $RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O;

(iii) $(PhO)_2P(O)N_3$, Et_3N, toluene, reflux;

(iv) MeOH, toluene, reflux;

(v) 6*N* HCl, 1,4-dioxane.

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid methyl ester

Trimethylsilyldiazomethane (31.5 mL of a 2 M solution in hexanes, 63 mmol) was added dropwise to a stirring solution of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid (10 g, 43 mmol) in toluene (80 mL) and methanol (20 mL) at 0°C under argon, and the mixture was allowed to warm to room temperature. The mixture was stirred for 1 hour, and then the solvent was evaporated under reduced pressure. The residue was taken up in ethyl acetate (50 mL), washed with saturated sodium hydrogen carbonate solution, dilute hydrochloric acid, dried

($MgSO_4$), and the solvent removed *in vacuo* to give 10.6 g (100%) of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid methyl ester;

R_f (heptane-ethyl acetate, 9:1) 0.40;

IR thin film (cm^{-1}) 1736 (C=O);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.30-7.18 (5H, m, Ph), 3.69 (3H, s, OMe), 2.78 (1H, d, *J* 13.4, $CH_AH_BCO_2Me$), 2.72 (1H, d, *J* 13.4, $CH_AH_BCO_2Me$), 2.28 (2H, s, CH_2Ph), 2.16-1.50 (5H, m), 1.30-1.03 (2H, m), 1.00 (3H, d, *J* 6.6, Me).

((1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid methyl ester (10.5 g, 43 mmol) and sodium periodate (128.0 g, 598 mmol) were stirred together in carbon tetrachloride (120 mL), acetonitrile (120 mL), and water (210 mL) for 1 hour. The mixture was cooled to 10°C, and ruthenium(III) chloride (0.177 g, 0.86 mmol) was added to the reaction mixture. The reaction was allowed to warm to room temperature and stirred for 20 hours. Diethyl ether (100 mL) was added, and the mixture was acidified to pH 1 with concentrated hydrochloric acid and then extracted with ether (2 × 200 mL). The organic layer was extracted with saturated aqueous sodium hydrogen carbonate (2 × 200 mL) which was then acidified to pH 1 with 4N hydrochloric acid and re-extracted with ethyl acetate, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, eluting with a gradient of heptane to 1:1 heptane:ethyl acetate) to give 8.02 g (87.7%) of ((1S,3R)-1-methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid;

R_f (heptane-ethyl acetate, 1:1) 0.46;

IR thin film (cm^{-1}) 3100 (OH), 1737 (C=O), 1705 (C=O);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.68 (3H, s, OMe), 2.67-2.51 (4H, m), 2.06 (1H, m), 1.97-1.79 (2H, m), 1.76-1.59 (2H, m), 1.29-1.08 (2H, m), 1.01 (3H, d, *J* 6.6, Me);

MS (ES^+) *m/z* 215 (M+H), 278 (M+Na, 100), 451 (2M+Na, 80%).

((1R,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester

Diphenylphosphoryl azide (8.07 mL, 37.4 mmol), triethylamine (5.36 mL, 39 mmol), and ((1S,3R)-1-methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid (7.93 g, 37 mmol) were refluxed in toluene (80 mL) for 17 hours. The mixture was allowed to cool and then taken up in ethyl acetate (250 mL), washed with saturated aqueous sodium hydrogen carbonate (250 mL), brine (100 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 7.82 g (100%) of ((1R,3R)-1-isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester which was used without further purification;

IR thin film (cm^{-1}) 2264 (CN), 1732 (C=O).

[(1R,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester

((1R,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester (7.82 g, 37 mmol) was refluxed in methanol (30 mL) and toluene (80 mL) for 17 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, heptane to heptane:ether 8:2) to give 2.60 g (29%) of [(1R,3R)-1-(methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester;

R_f (heptane-ethyl acetate, 1:1) 0.52;

IR thin film (cm^{-1}) 1728 (C=O), 1716 (C=O);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.67 (6H, s, OMe, $NHCO_2$*Me*), 3.21 (1H, dd, *J* 7.08, 14.2, CH_AH$_B$NHCO2Me), 3.11 (1H, dd, *J* 6.10, 13.9, CH$_A$*H$_B$*NHCO$_2$Me), 2.36 (2H, s, CH_2CO$_2$Me), 2.05 (1H, m, C*H*Me), 1.86-1.46 & 1.29-1.18 (5H, m), 0.99 (3H, d, *J* 6.59, Me).

((1R,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride

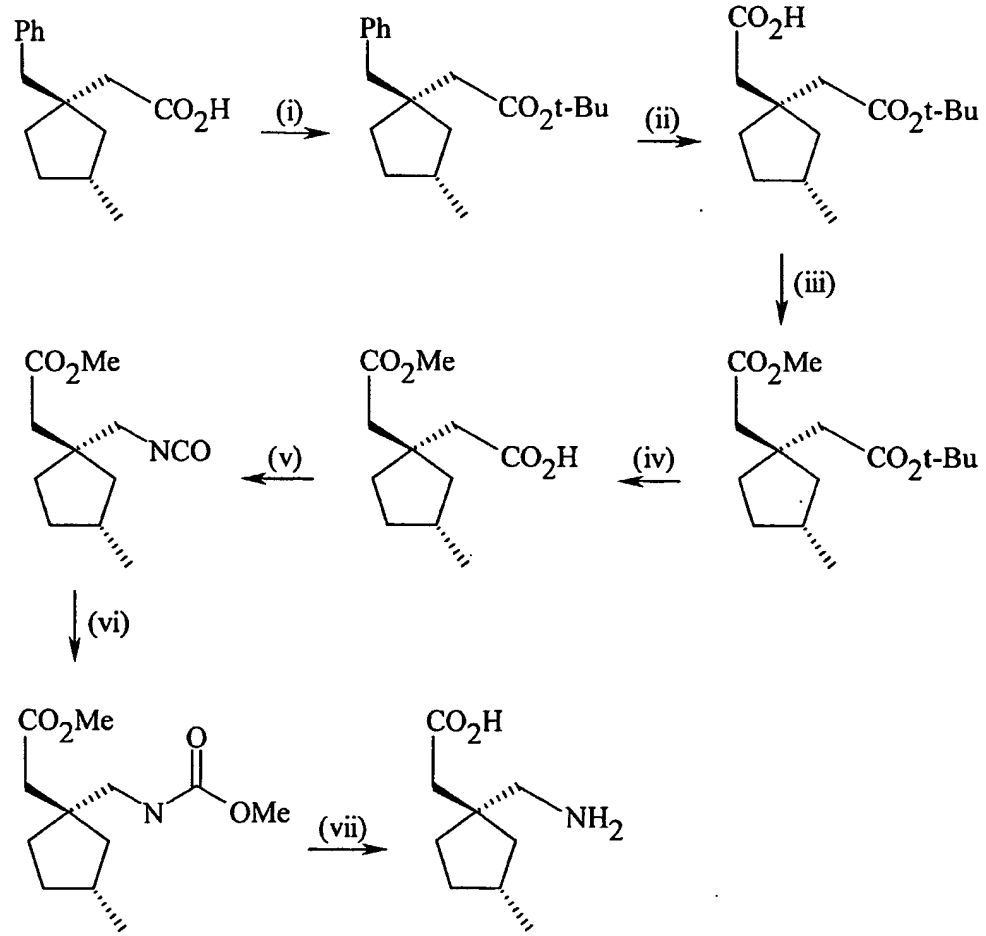
[(1R,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester (2.60 g, 37 mmol) was refluxed in a mixture of 1,4-dioxane (15 mL)

and 6N Hydrochloric acid (30 mL) for 16 hours. The mixture was allowed to cool, diluted with water (80 mL), and washed with dichloromethane (2 x 200 mL). The aqueous layer was evaporated under reduced pressure, and the residue was recrystallized from ethyl acetate/methanol (95:5) to give 0.55 g (25%) of ((1R,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

IR thin film (cm^{-1}) 1724 (C=O);

^{1}H-NMR (400 MHz; DMSO-d_6): δ 2.92 (1H, d, *J* 12.9, CH_AH$_B$N), 2.87 (1H, d, *J* 12.9, CH$_A$$H_B$N), 2.45 (1H, d, *J* 15.9, CH_AH$_B$COOH), 2.40 (1H, d, *J* 15.9, CH$_A$$H_B$COOH), 1.95 (1H, m), 1.84-1.72 (2H, m), 1.60-1.48 (2H, m), 1.20 (1H, m), 1.04 (1H, m), 0.96 (3H, d, *J* 6.8, Me).

EXAMPLE 3



(i) a) oxalyl chloride, DMF, CH_2Cl_2; b) *t*-BuOH, (*i*-Pr)$_2$Net, CH_2Cl_2;

(ii) $RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O;

(iii) $(CH_3)_3SiCHN_2$, MeOH, toluene;

(iv) CF_3CO_2H, CH_2Cl_2;

(v) $(PhO)_2P(O)N_3$, Et_3N, toluene, reflux;

(vi) MeOH, toluene, reflux;

(vii) 6*N* HCl, 1,4-dioxane.

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid *tert*-butyl ester

Oxalyl chloride (4.14 mL, 47 mmol) was added dropwise to a stirring solution of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid (10 g, 43 mmol) in dichloromethane under argon at room temperature. The reaction mixture was cooled to 5°C, dimethylformamide (1 mL) was carefully added, and the mixture was allowed to warm to room temperature and stirred for a further 2 hours. The solvent was removed *in vacuo* and the residue diluted with dichloromethane (60 mL). 1,1-Dimethylethanol (15 mL) was carefully added to the reaction mixture under argon followed by diisopropylethylamine (11.5 mL, 65 mmol). The mixture was stirred for 17 hours and then taken up in ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate (2 × 200 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, eluting with a gradient of heptane to 9:1 heptane:ethyl acetate) to give 10.92 g (88%) of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid *tert*-butyl ester;

R_f (heptane-ethyl acetate, 9:1) 0.64;

IR thin film (cm^{-1}) 1724 (C=O);

^{1}H-NMR (400 MHz;$CDCl_3$): δ 7.29-7.17 (5H, m, Ph), 2.77 (1H, d, *J* 13.6, CH_AH_BPh), 2.71 (1H, d, *J* 13.6, CH_AH_BPh), 2.18 (1H, s, $CH_AH_BCO_2{}^t$Butyl), 2.17 (1H, s,$CH_AH_BCO_2{}^t$Butyl) , 1.49 (9H, s, CMe_3), 2.17-1.5 & 1.30-1.00 (7H, m), 1.00 (3H, d, *J* 6.8, CH*Me*).

[(1S,3R)-1-Carboxymethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid *tert*-butyl ester (10.72 g, 37.2 mmol) and sodium periodate (124.77 g, 0.583 mol) were stirred together in carbon tetrachloride (120 mL), acetonitrile (120 mL), and water (210 mL) for 2 hours. The mixture was cooled to 0°C, and ruthenium(III) chloride (0.173 g, 0.83 mmol) was added to the reaction mixture. The reaction was allowed to warm to room temperature and stirred for 48 hours. Diethyl ether (60 mL) was added, and the mixture was then acidified to pH 2 by the addition of dilute hydrochloric acid. The mixture was extracted with ethyl acetate (2 × 200 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, eluting with a gradient of heptane to 1:1 heptane:ethyl acetate) to give 7.01 g (73.5%) of [(1S,3R)-1-carboxymethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester;

R_f (heptane-ethyl acetate, 1:1) 0.58;

IR thin film (cm^{-1}) 2953 (OH), 1726 (C=O) 1705 (C=O);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.51 (2H, s, CH_2CO), 2.46 (2H, s, CH_2CO), 1.47 (9H, s, CMe_3), 2.05-2.15, 1.95-1.80, 1.75-1.60, 1.30-1.03 (7H, m), 1.01 (3H, d, *J* 6.4, Me).

[(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester

Trimethylsilyldiazomethane (14 mL of a 2 M solution in hexanes, 26.9 mmol) was added dropwise to a stirring solution of [(1S,3R)-1-carboxymethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester (6.9 g, 26.9 mmol) in toluene (60 mL) and methanol (15 mL) at 10°C under argon, and the mixture was allowed to warm to room temperature. The mixture was stirred for 2 hours, and then the solvent was evaporated under reduced pressure. The residue was taken up in ethyl acetate (200 mL), washed with saturated sodium hydrogen carbonate solution, dilute hydrochloric acid, dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was purified by chromatography (silica gel, eluting with a gradient of heptane to 95:5 heptane:ethyl acetate) to give 6.73 g (92.4%) of [(1S,3R)-1-methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester;

R_f (heptane-ethyl acetate, 9:1) 0.36;

IR thin film (cm^{-1}) 1738 (C=O) 1732 (C=O);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.65 (3H, s, OMe), 2.52 (2H, m, CH_2CO_2), 2.45 (1H, d, *J* 4.8, CH_2CO_2), 1.44 (9H, s, CMe_3), 2.05-1.5, 1.30-1.10 (7H, m), 1.00 (3H, d, *J* 6.8, Me).

((1R,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid

[(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester (6.64 g, 24.6 mmol) and trifluoroacetic acid (10 mL) were stirred together in dichloromethane (30 mL) for 17 hours at room temperature. The mixture was carefully poured into aqueous sodium carbonate and extracted with ethyl acetate (200 mL). The aqueous was acidified to pH 1 with concentrated hydrochloric acid and re-extracted with ethyl acetate (3 × 200 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, eluting with a gradient of heptane to 1:1 heptane:ethyl acetate) to give 5.26 g (100%) of [(1R,3R)-1-methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid;

R_f (heptane-ethyl acetate, 1:1) 0.46;

IR thin film (cm^{-1}) 2952 (OH), 1737 (C=O), 1706(C=O);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.68 (3H, s, OMe), 2.67 (1H, d, *J* 15.0, $CH_AH_BCO_2$), 2.61 (1H, d, *J* 14.9, $CH_AH_BCO_2$), 2.58 (1H, d, *J* 14.8, $CH_AH_BCO_2$), 2.53 (1H, d, *J* 14.8, $CH_AH_BCO_2$), 1.93-1.81, 1.75-1.59, 1.75-1.63 (6H, m), 1.16 (1H, dd, *J* 19.5, 9.3), 1.01 (3H, d, *J* 6.35, Me).

((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester

Diphenylphosphoryl azide (5.35 mL, 24.8 mmol), triethylamine (3.55 mL, 25.6 mmol), and [(1R,3R)-1-methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid (5.26 g, 24.5 mmol) were refluxed in toluene (80 mL) for 17 hours. The mixture was allowed to cool and then taken up in ethyl acetate (300 mL), washed with saturated aqueous sodium hydrogen carbonate solution (250 mL), brine (200 mL), and dried ($MgSO_4$). The solvent was removed under reduced

pressure to give 5.19 g (100%) of ((1S,3R)-1-isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester which was used without further purification; IR thin film (cm^{-1}) 2262 (NCO), 1732 (C=O).

[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester

((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester (5.19 g, 24.5 mmol) was refluxed in methanol (30 mL) and toluene (80 mL) for 17 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, heptane-ethyl acetate 9:1) to give 4.62 g (77%) of [(1S,3R)-1-(methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester; R_f (heptane-ethyl acetate, 1:1) 0.59;

IR thin film (cm^{-1}) 1730 (C=O);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.68 (6H, s, O*Me*, $NHCO_2$*Me*), 3.27 (1H, dd, *J* 13.7, 6.8, C*H*$_A$H$_B$NHCO$_2$Me), 3.13 (1H, dd, *J* 13.9, 6.4, CH$_A$*H*$_B$NHCO$_2$Me), 2.37 (1H, d, *J* 13.9, C*H*$_A$H$_B$CO$_2$), 2.33 (1H, d, *J* 13.9, CH$_A$*H*$_B$CO$_2$), 2.09-1.99 (1H, m, C*H*Me), 1.88-1.76, 1.69-1.43, 1.28-1.19 (6H, m), 1.01 (3H, d, *J* 6.4, Me); *m/z* (CI^+) 244 (M+H, 100%).

((1S,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride

[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester (2.84 g, 11.7 mmol) was refluxed in a mixture of 1,4-dioxane (15 mL) and 6N Hydrochloric acid (30 mL) for 17 hours. The mixture was allowed to cool, diluted with water (200 mL), and washed with dichloromethane (2 × 100 mL). The aqueous layer was evaporated under reduced pressure, and the residue was recrystallized from ethyl acetate/methanol (95:5) to give 1.28 g (53%) of ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

IR thin film (cm^{-1}) 1710 (C=O);

^{1}H-NMR (400 MHz; DMSO-d_6): δ 2.96 (1H, d, J 12.8, CH_AH$_B$NH$_2$), 2.90 (1H, d, J 12.8, CH$_A$$H_BNH_2$), 2.40 (2H, s, C$H_2$COOH), 2.09-1.98 (1H, m, CHMe), 1.81-1.61, 1.51-1.43, 1.21-1.11(5H, m), 1.04 (1H, dd, J 13.2, 10.4), 0.97 (3H, d, J 6.35, Me);

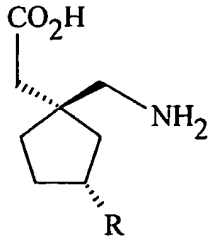
MS (ES$^+$) *m/z* 173 (M+H, 100%), 196 (M+Na, 10%);

LCMS (Prodigy® ODS 3 50 mm × 4.6 mm id column, 5% for 2 min, 5-50% over 1.5 min of acetonitrile (0.05% formic acid)/water (0.05% formic acid)) Retention Time = 0.92, 94% de; (Found: C, 49.5; H, 8.78; N, 6.37.

$C_9H_{17}NO_2$ 1HCl 0.6H_2O requires C, 49.5; H, 8.86; N, 6.41).

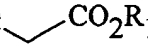
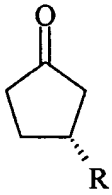
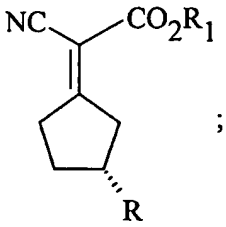
CLAIMS

1. A process for the preparation of a compound of Formula I

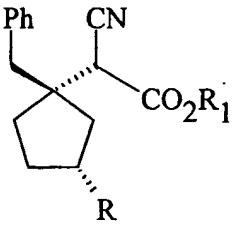


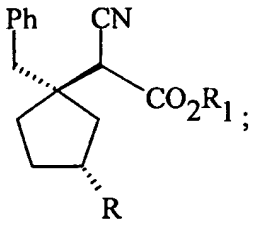
I

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

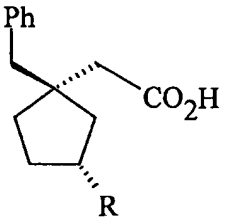
a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (1)  , a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (2)  ;

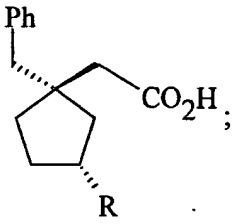
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition

products of formulas (3a)  and (3b)

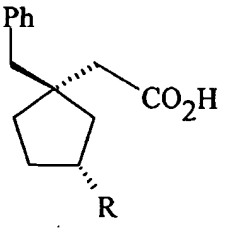
 ;

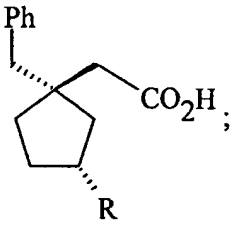
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, or cesium hydroxide in a solvent and stirring, and then acidifying to

produce the carboxylic acids of formulas (4a) 

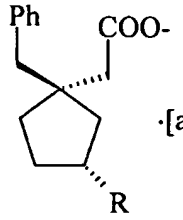
and (4b)  ; or

adding the products of Step b) above to an acid mixture and stirring

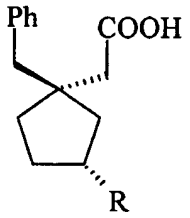
to produce the carboxylic acids of formulas (4a) 

and (4b)  ;

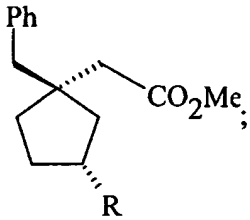
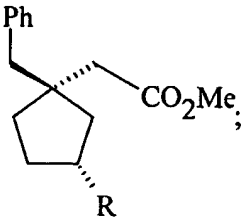
d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

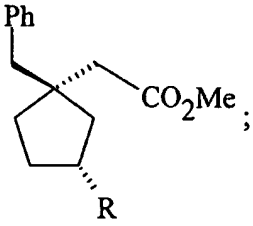
diastereomer of formula (5)  ·[amine-H]$^+$ as the amine salt;

e) converting the product of Step d) to a carboxylic acid of formula (6)

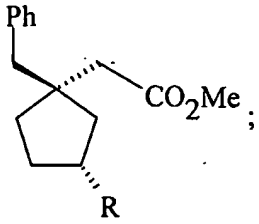
 ;

f) adding the product of Step e) to a mixture of iodomethane, a solvent, and a base, and stirring to produce the ester of formula (7)

 ; or adding the product of Step e) to methanol and an acid to produce the ester of formula (7)  ;

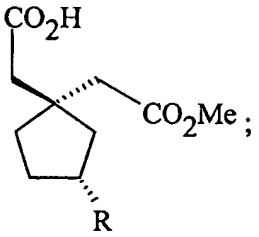
or adding the product of Step e) above to trimethylsilyldiazomethane and methanol in a solvent to produce the ester of formula (7)  ;

or adding the product of Step e) to a solution of diazomethane or trimethylsilyl-diazomethane in a solvent to produce ester of

formula (7) 

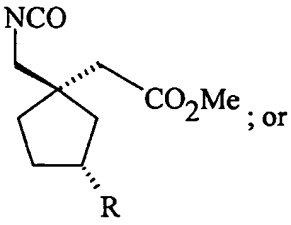
;

g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of

formula (8) 

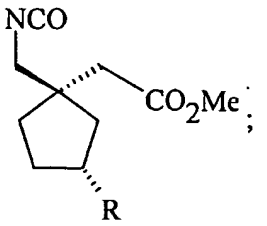
;

h) adding the product of Step g) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to

produce the isocyanate of formula (9) 

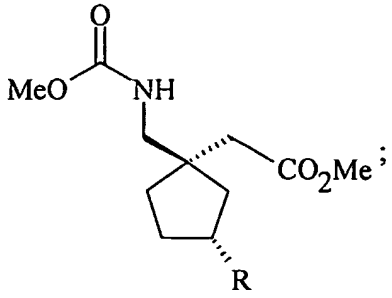
; or

adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate of formula (9)

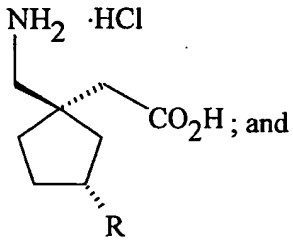


;

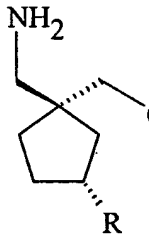
i) adding the product of Step h) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (10)



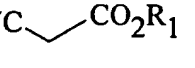
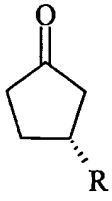
j) adding the product of Step i) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of

formula (Ia)  ; and

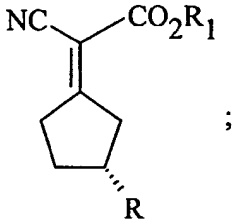
k) converting the product of Step j) to a compound of formula (I)

 , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

2. A process according to Claim 1 which comprises:

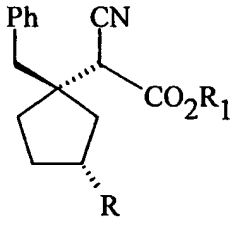
a) adding a cyanoacetate of formula (A)  wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of formula (1)  , a solvent selected from

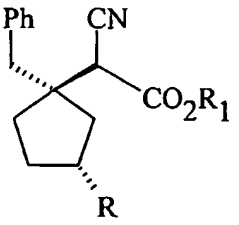
tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)



;

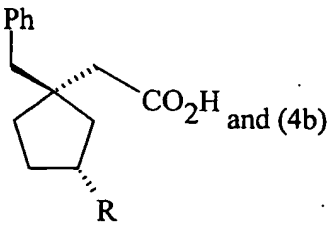
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce the addition products of

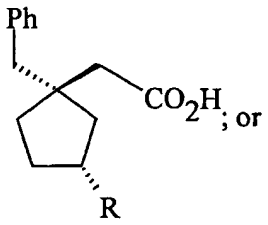
formulas (3a) 

and (3b) 

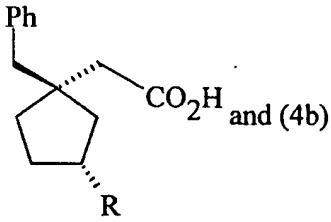
;

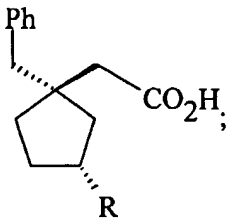
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture, and then acidifying to produce the carboxylic

acids of formulas (4a)  and (4b)

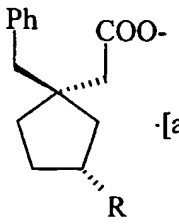


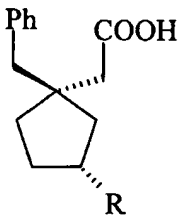
adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H_2SO_4, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the

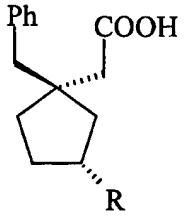
carboxylic acids of formulas (4a)  and (4b)



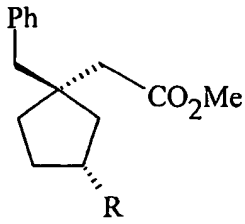
d) contacting the products of Step c) above with an amine selected from (S)-α-methyl-benzylamine, (R)-α-methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and

1,4-dioxane, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$ as the amine salt;

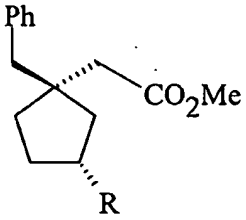
e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid to which water is added and stirring to produce the carboxylic acid of formula (6)  ; or

partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of formula (6)  ;

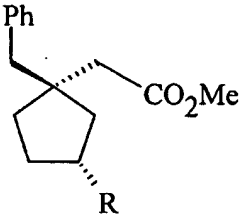
f) adding the product of Step e) above to a mixture of iodomethane, a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene, and 1,4-dioxane, and a base selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine, triethylamine, and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and stirring at a temperature of from -40°C to 110°C to produce the ester

of formula (7)  ; or adding the product of Step e)

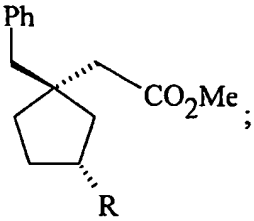
above to a mixture of methanol and concentrated sulphuric acid, concentrated hydrochloric acid, or hydrogen chloride at a temperature of from 0°C to 100°C to produce the ester of formula (7)

 ; or adding the product of Step e) above to

trimethylsilyldiazomethane and methanol in benzene or toluene at a temperature of from -40°C to 100°C to produce the ester of

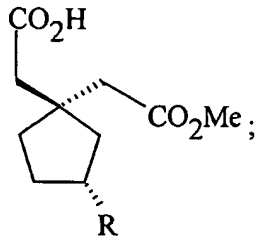
formula (7)  ; or adding the product of Step e)

above to diazomethane or trimethylsilyldiazomethane in a solvent selected from benzene, toluene, dichloromethane, and diethyl ether at a temperature of from -40°C to 40°C to give a compound of

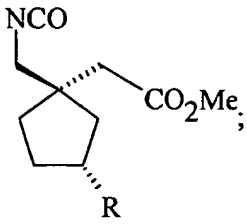
formula (7)  ;

g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to

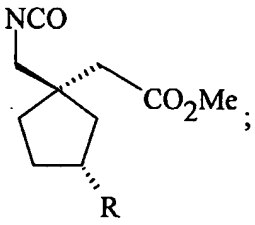
80°C to produce the carboxylic acid of formula (8)



h) adding the product of Step g) above to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene, benzene, xylenes, tetrahydrofuran, diethyl ether and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature of from 0°C to 150°C to produce the isocyanate of formula (9)



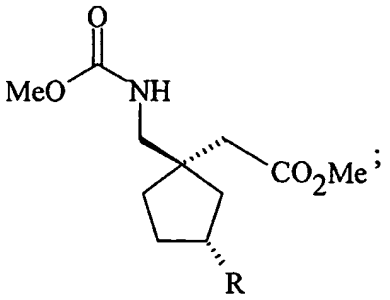
; or adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate, a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate of formula (9)



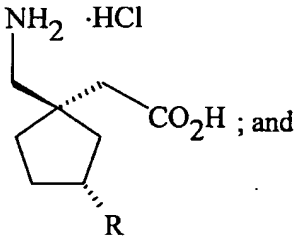
;

i) adding the product of Step h) to a mixture of a solvent selected from toluene, benzene, xylenes and *n*-heptane, and methanol, and stirring

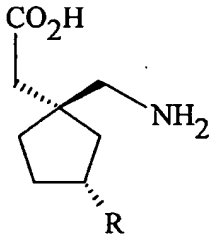
at a temperature from 0°C to 150°C to produce the carbamate of

formula (10)  ;

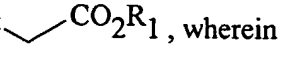
j) adding the product of Step i) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from 0°C to 115°C to produce a compound of formula Ia

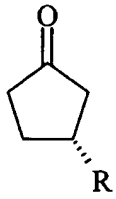
 ; and

k) converting the product of Step j) to a compound of Formula I

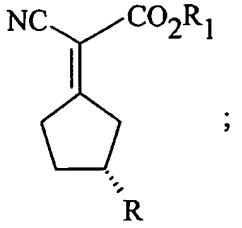
 , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

3. A process according to Claim 1 which comprises:

a) adding a cyanoacetate of formula (A)  , wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)

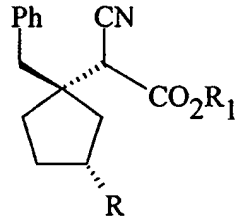
 , toluene, acetic acid, and a Knoevenagel reaction catalyst

which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)

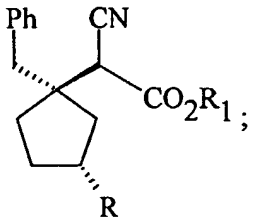


;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition products of formulas (3a)

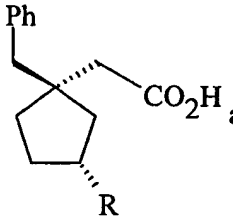


and (3b)

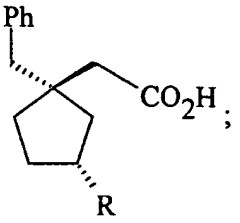


;

c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of formulas (4a)

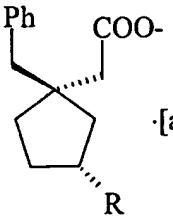


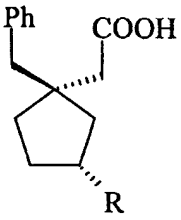
and (4b)

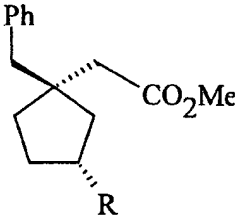


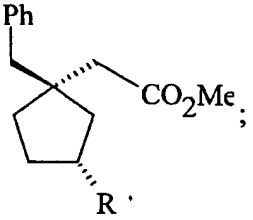
;

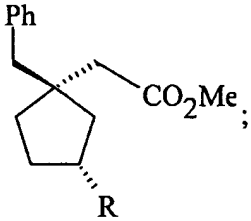
d) contacting the products of Step c) above with (S)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of

formula (5)  ·[amine-H]$^+$ as the (S)-α-methyl-benzylamine salt;

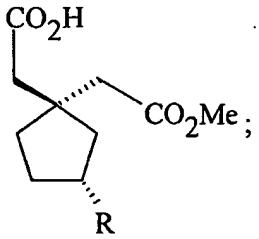
e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (6)  ;

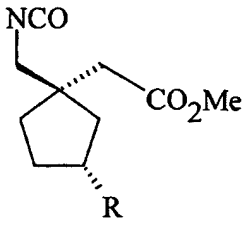
f) adding the product of Step e) to a mixture of iodomethane, dichloromethane, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and stirring to produce the ester of formula (7)  ;

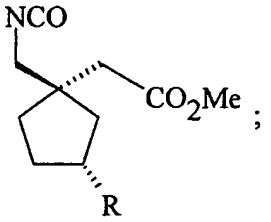
or adding the product of Step e) to methanol and concentrated sulfuric acid to produce the ester of formula (7)  ;

or adding the product of Step e) to a solution of diazomethane or trimethylsilyl-diazomethane in dichloromethane to produce the ester of formula (7)  ;

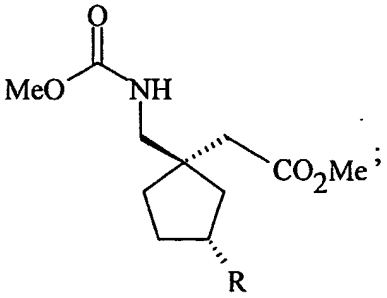
g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and

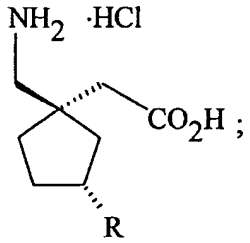
ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (8)  ;

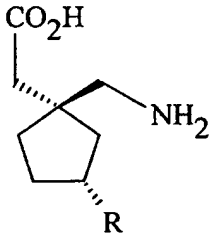
h) adding the product of Step g) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the isocyanate of formula (9)  ; or adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate and triethylamine in tetrahydrofuran at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran, followed by adding toluene or benzene, and refluxing to produce ester of formula (9)

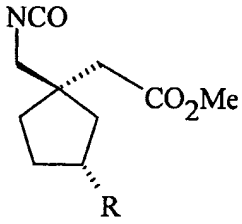
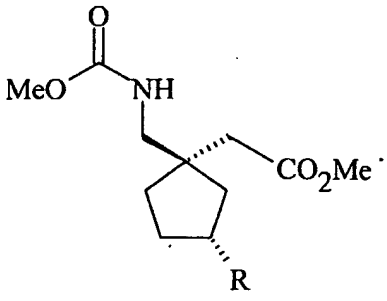
 ;

i) adding the product of Step h) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (10)

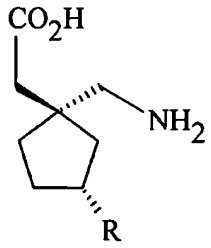
 ;

j) adding the product of Step i) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a compound of formula Ia  ;

k) converting the product of Step j) to a compound of Formula I  , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

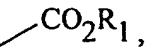
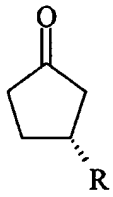
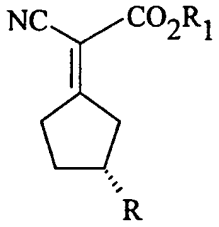
4. A process according to Claim 1, further characterized in that the intermediate product (9)  formed is reacted, without isolation, with methanol to produce the carbamate of formula (10) 

5. A process for the preparation of a compound of Formula II

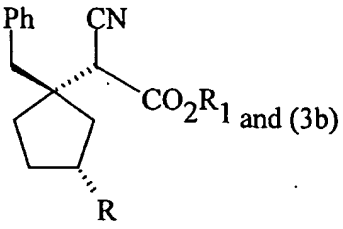


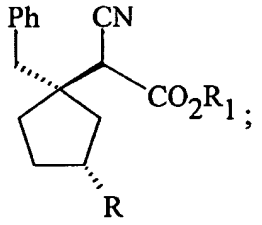
II

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

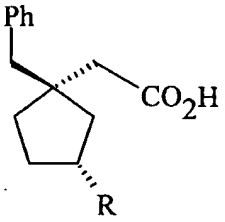
a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (1)  , a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (2)  ;

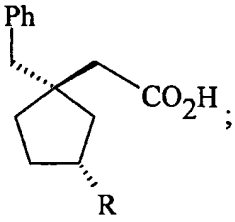
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition

products of formulas (3a)  and (3b)

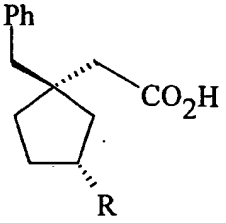
 ;

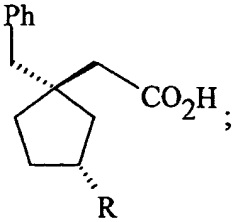
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide and a solvent, and stirring, and then acidifying

to produce the carboxylic acids of formulas (4a) 

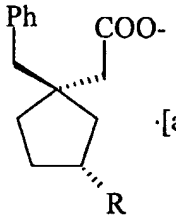
and (4b)  ; or

adding the products of Step b) above to an acid mixture and stirring

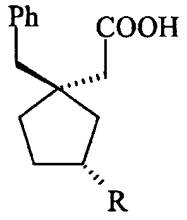
to produce the carboxylic acids of formulas (4a) 

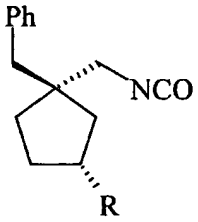
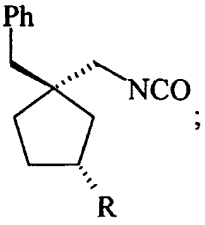
and (4b)  ;

d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

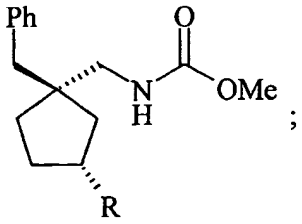
diastereomer of formula (5)  ·[amine-H]$^+$ as the amine salt; and

e) converting the product of Step d) to a carboxylic acid of formula (6)

 ;

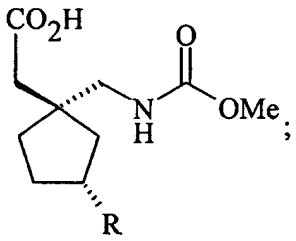
f) adding the product of Step e) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the isocyanate of formula (11)  ; or adding the product of Step e) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (11)  ;

g) adding the product of Step f) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (12)



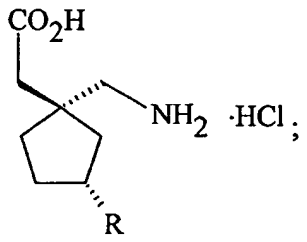
;

h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (13)



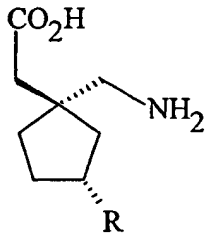
;

i) adding the product of Step h) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (IIa)



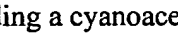
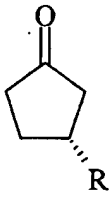
;

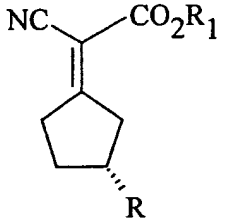
j) converting the product of Step i) to a compound of formula (II)



, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

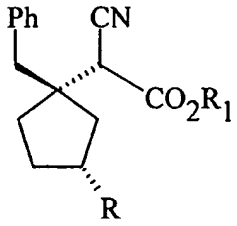
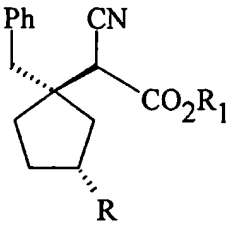
6. A process according to Claim 5 which comprises:

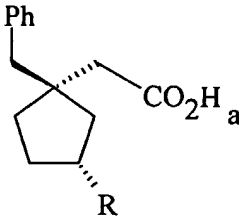
a) adding a cyanoacetate of formula (A)  wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of formula (1)  , a solvent selected from tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

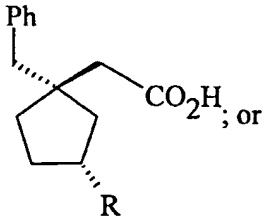


;

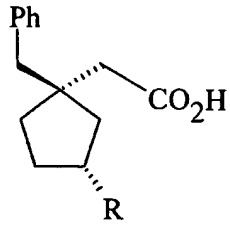
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and

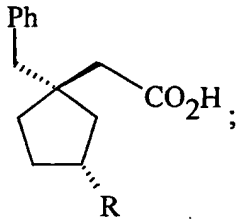
tert-butyl methyl ether to produce the addition products of formulas (3a)  and (3b)  ;

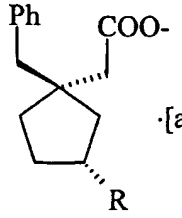
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture and then acidifying to produce the carboxylic acids of formulas (4a)  and (4b)



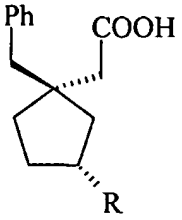
adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H_2SO_4, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the

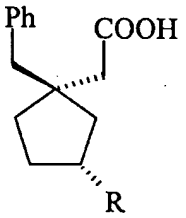
carboxylic acids of formulas (4a)  and (4b)

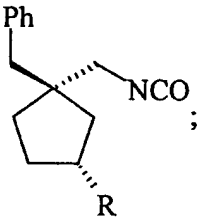
 ;

d) contacting the products of Step c) above with an amine selected from (S)-α-methyl-benzylamine, (R)-α-methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$ as the amine salt;

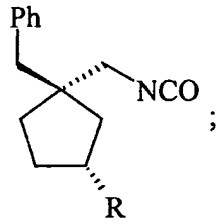
e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid

dissolved in acetic acid and water, and stirring to produce the carboxylic acid of formula (6)  ; or

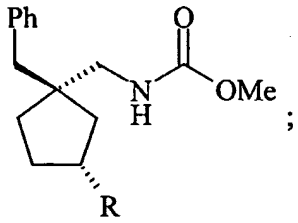
partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of formula (6)  ;

f) adding the product of Step e) above to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene, benzene, xylenes, tetrahydrofuran, diethyl ether and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature of from 0°C to 150°C to produce the isocyanate of formula (11)  ; or adding the product of Step e) above to ethyl chloroformate or isobutyl chloroformate and a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene

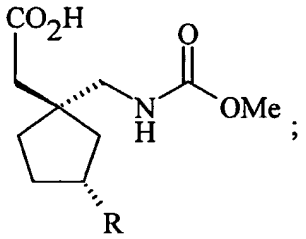
or benzene, and refluxing to produce the isocyanate of formula (11)



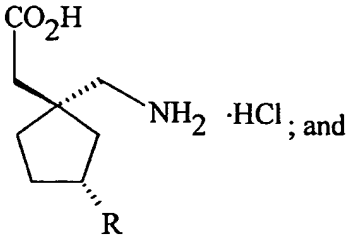
g) adding the product of Step f) to a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and methanol, and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (12)



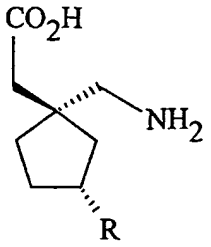
h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (13)



i) adding the product of Step h) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from 0°C to 115°C to produce a compound of formula IIa

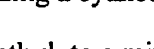


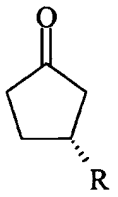
j) converting the product of Step i) to a compound of Formula II



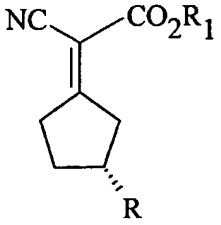
, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

7. A process according to Claim 5 which comprises:

a) adding a cyanoacetate of formula (A)  , wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)

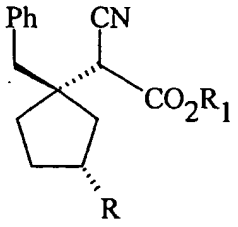


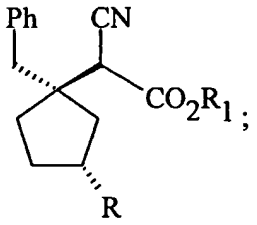
, toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)



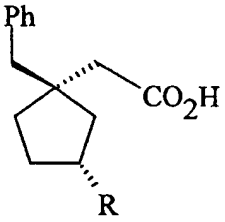
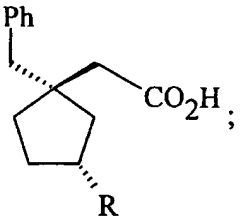
;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C

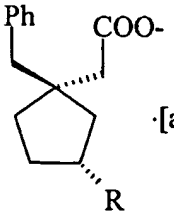
to produce the addition products of formulas (3a) 

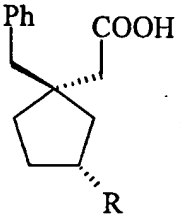
and (3b)  ;

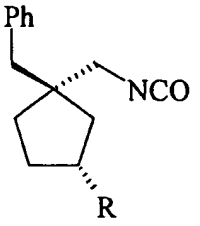
c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of

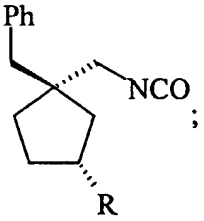
formulas (4a)  and (4b)  ;

d) contacting the products of Step c) above with (S)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of

formula (5)  ·[amine-H]$^+$ as the (S)-α-methyl-benzylamine salt;

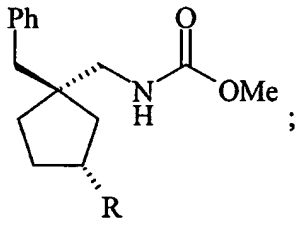
e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (6)  ;

f) adding the product of Step e) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the isocyanate of formula (11) 

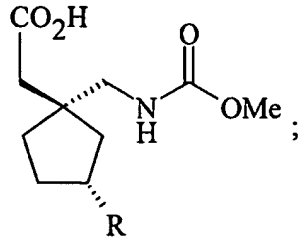
; or adding the product of Step e) above to ethyl chloroformate or isobutyl chloroformate and triethylamine in tetrahydrofuran at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (11) 

;

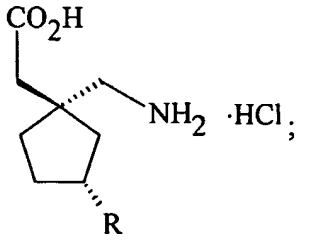
g) adding the product of Step f) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (12)

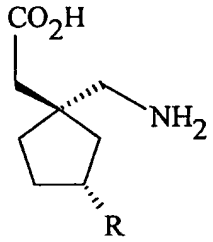


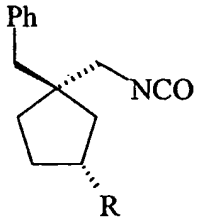
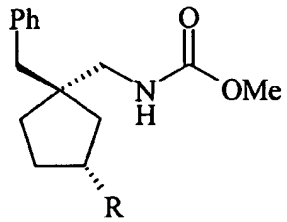
;

h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (13) 

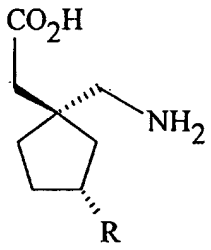
;

i) adding the product of Step h) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a compound of formula IIa  ;

j) converting the product of Step i) to a compound of Formula II  , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

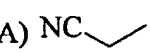
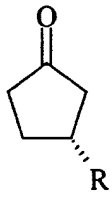
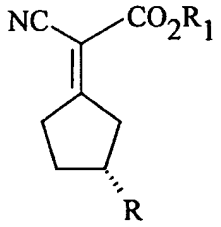
8. A process according to Claim 5, further characterized in that the intermediate product (11)  formed is further reacted, without isolation, with methanol to produce the carbamate of formula (12)  .

9. A process for the preparation of a compound of Formula II

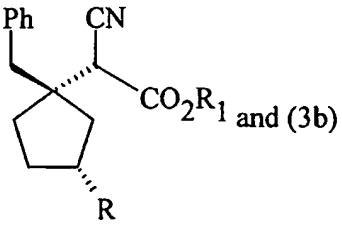


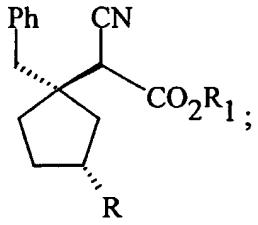
II

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

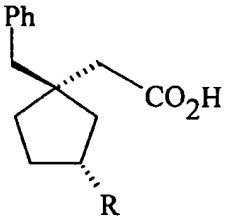
a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (1)  , a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (2)  ;

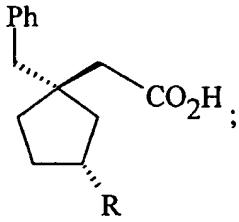
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition

products of formulas (3a)  and (3b)

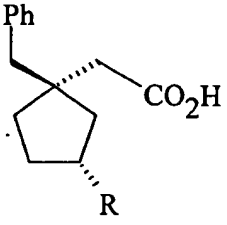
 ;

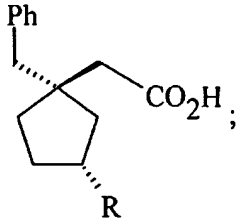
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying

to produce the carboxylic acids of formulas (4a) 

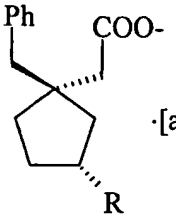
and (4b)  ; or

adding the products of Step b) above to an acid mixture and stirring

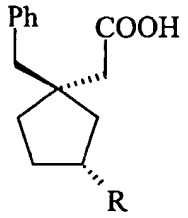
to produce the carboxylic acids of formulas (4a) 

and (4b)  ;

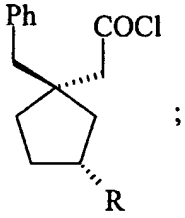
d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

diastereomer of formula (5)  ·[amine-H]$^+$ as the amine salt;

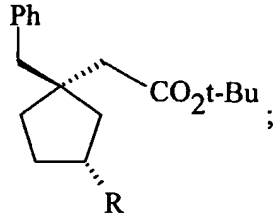
e) converting the product of Step d) to a carboxylic acid of formula (6)

 ;

f) adding oxalyl chloride to a mixture of the product of Step e), a solvent, and N,N-dimethylformamide (DMF), and stirring to produce

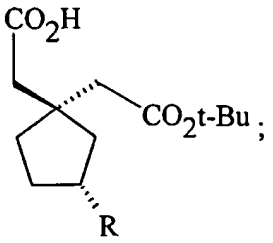
the acid chloride of formula (14)  ;

g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent, and a tertiary amine base, and stirring to produce the ester of

formula (15)  ;

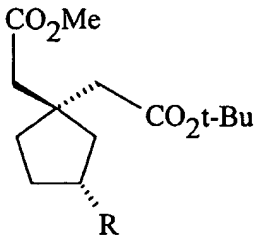
h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and

ruthenium(III) chloride, and stirring to produce the carboxylic acid of

formula (16) 

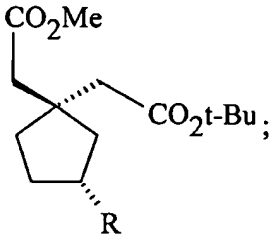
;

i) adding the product of Step h) to a mixture of a solvent, methanol, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of

formula (17) 

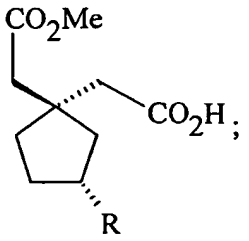
; or adding the product of Step h)

to a mixture of iodomethane, a solvent, and a base, and stirring to

produce the bis ester of formula (17) 

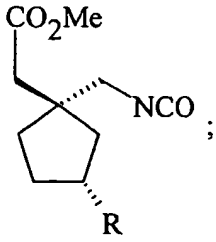
;

j) adding an acid to a mixture of the product from Step i) and a solvent, and stirring to produce the carboxylic acid of formula (18)

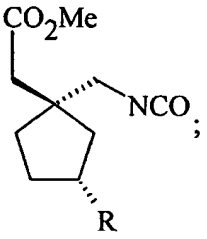


;

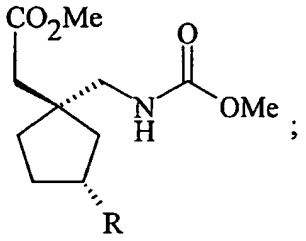
k) adding the product of Step j) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA) is added, and stirring

to produce the isocyanate of formula (19)  ; or

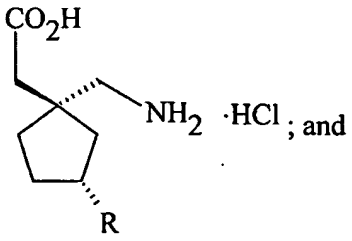
adding the product of Step j) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene,

and refluxing to produce isocyanate of formula (19)  ;

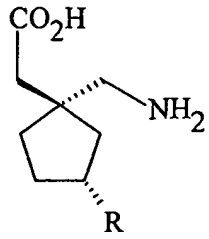
l) adding the product of Step k) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (20)

 ;

m) adding the product of Step l) to a mixture of a solvent and aqueous hydrochloric acid is added, and stirring to produce a compound of

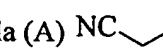
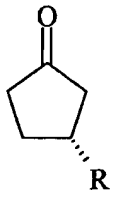
formula (IIa)  ; and

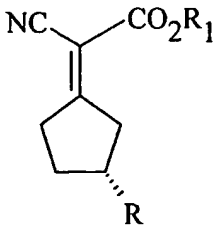
n) converting the product of Step m) to a compound of formula (II)



, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

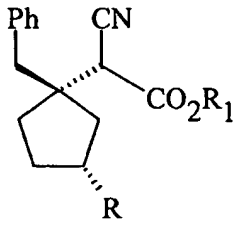
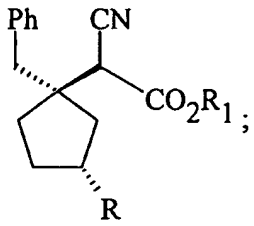
10. A process according to Claim 9 which comprises:

a) adding a cyanoacetate of formula (A)  wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of formula (1)  , a solvent selected from tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

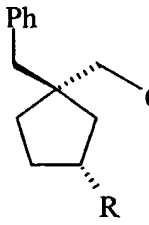


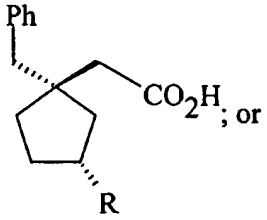
;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce the addition products of

formulas (3a)  and (3b)  ;

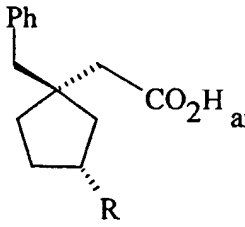
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture and then acidifying to produce the carboxylic

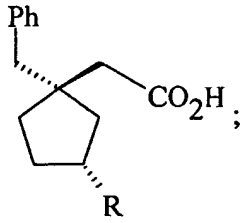
acids of formulas (4a)  and (4b)

 ;

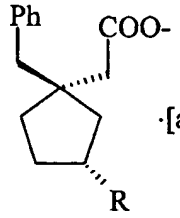
or

adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H_2SO_4, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the

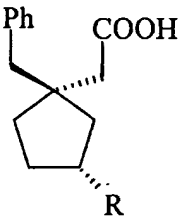
carboxylic acids of formulas (4a)  and (4b)

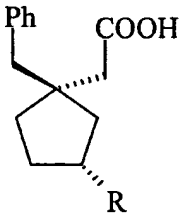
 ;

d) contacting the products of Step c) above with an amine selected from (S)-α-methyl-benzylamine, (R)-α-methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the

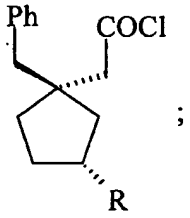
enriched diastereomer of formula (5)  ·[amine-H]$^+$ as the amine salt;

e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid

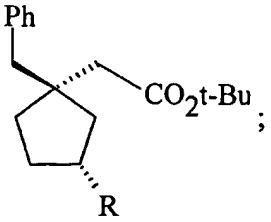
dissolved in acetic acid and water, and stirring to produce the carboxylic acid of formula (6)  ; or

partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of formula (6)  ;

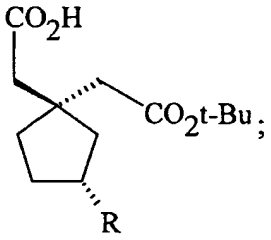
f) adding oxalyl chloride to a mixture of the product of Step e), a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, and *tert*-butyl methyl ether, and 0.01 to 10 mole percent of N,N-dimethylformamide (DMF), and stirring at a temperature from -40°C to 110°C to produce the acid chloride of formula (14)

 ;

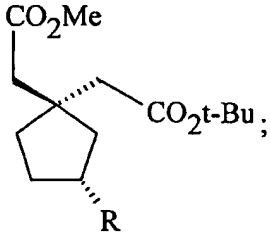
g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, and *tert*-butyl methyl ether, and *N,N*-diisopropylethylamine

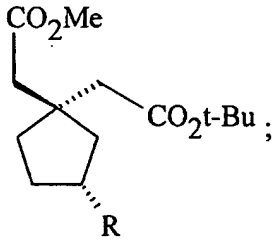
(DIPEA) or triethylamine, and stirring at a temperature from -40°C to 110°C to produce the ester of formula (15)  ;

h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (16)

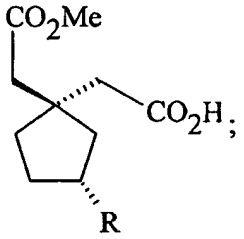
 ;

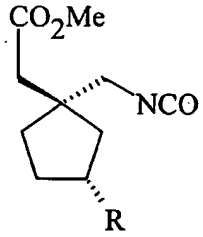
i) adding the product of Step h) to a solvent selected from toluene, benzene, xylenes, and *n*-heptane, methanol, and (trimethylsilyl)diazomethane, and stirring at a temperature from 0°C to 150°C to produce the bis ester of formula (17)

 ; or adding the product of Step h) to a mixture of iodomethane, a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene and 1,4-dioxane, and a base selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine, triethylamine, or 1,5-diazabicyclo[4.3.0]non-

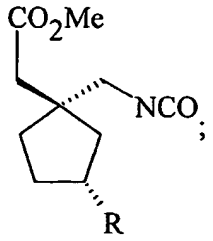
5-ene (DBN), and stirring at a temperature of from -40°C to 110°C to produce the bis ester of formula (17)  ;

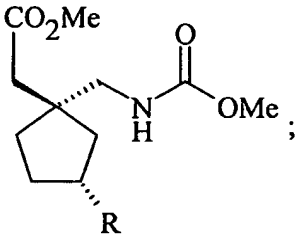
j) adding hydrochloric acid or trifluoroacetic acid (TFA) to a mixture of the product from Step i) and a solvent selected from dichloromethane, chloroform, 1,4-dioxane, tetrahydrofuran, ethyl ether, and *tert*-butyl methyl ether, and stirring at a temperature from -40°C to 110°C to produce the carboxylic acid of formula (18)

 ;

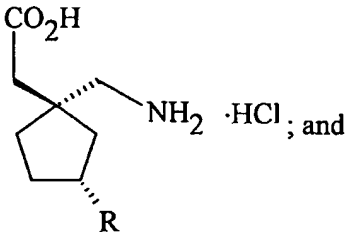
k) adding the product of Step j) to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature from 0°C to 150°C to produce the isocyanate of formula (19)  ; or adding the product of Step j) above to ethyl chloroformate or isobutyl chloroformate, a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and

tetrahydrofuran or acetone, followed by adding toluene or benzene,

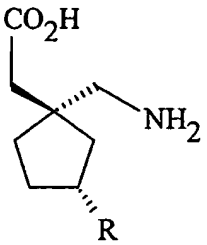
and refluxing to produce isocyanate of formula (19)  ;

l) adding the product of Step k) to a mixture of a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and methanol, and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (20)  ;

m) adding the product of Step l) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from 0°C to 115°C to produce a compound of formula IIa

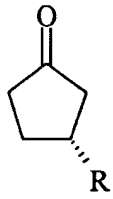
 ; and

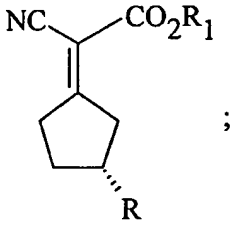
n) converting the product of Step m) to a compound of Formula II

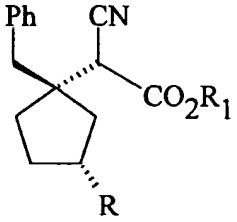
 , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

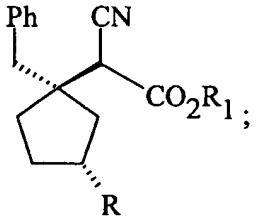
11. A process according to Claim 9 which comprises:

a) adding a cyanoacetate of formula (A) , wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)

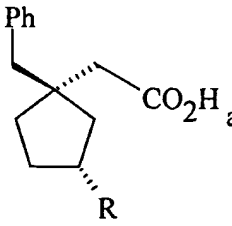
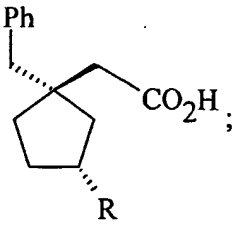
 , toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)

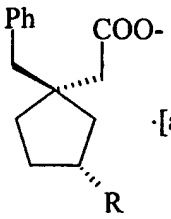
 ;

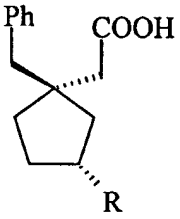
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition products of formulas (3a) 

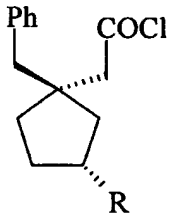
and (3b)  ;

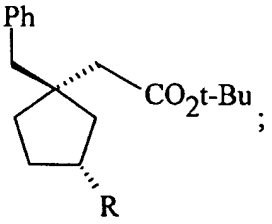
c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol and heating the mixture at 100°C to

200°C, and then acidifying to produce the hydrolysis products of formulas (4a)  and (4b)  ;

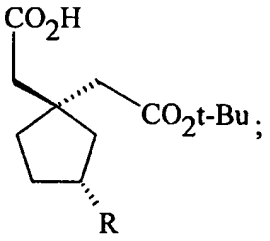
d) contacting the products of Step c) above with (S)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$ as the (S)-α-methyl-benzylamine salt;

e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (6)  ;

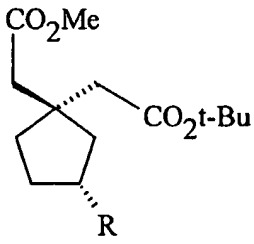
f) adding oxalyl chloride to a mixture of the product of Step e), dichloromethane, and a catalytic amount of N,N-dimethylformamide (DMF), and stirring to produce the acid chloride of formula (14)  ;

g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, dichloromethane, and *N,N*-diisopropylethylamine (DIPEA), and stirring to produce the ester of formula (15) 

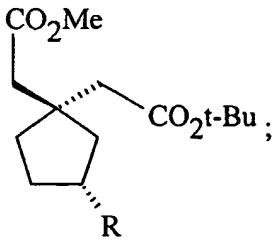
;

h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (16) 

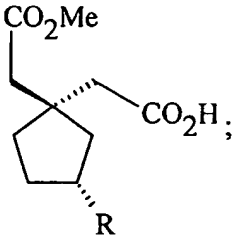
;

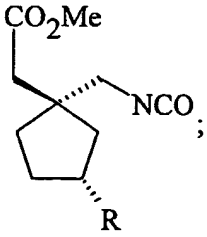
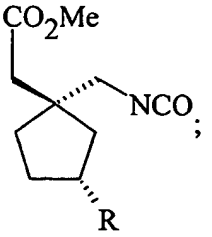
i) adding the product of Step h) to a mixture of methanol, toluene, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of formula (17) 

; or adding the product of Step h) to a mixture of iodomethane, dichloromethane, triethylamine, and stirring to produce the bis ester of formula (17)

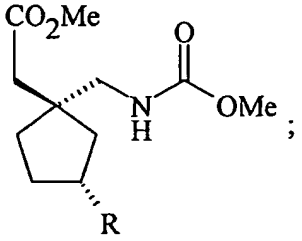


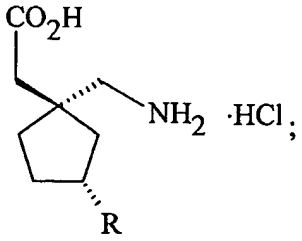
;

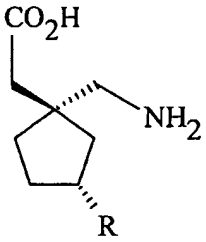
j) adding hydrochloric acid or trifluoroacetic acid (TFA) to a mixture of the product from Step i) and dichloromethane, and stirring to produce the carboxylic acid of formula (18)  ;

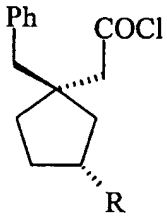
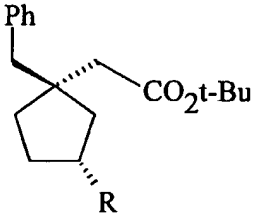
k) adding the product of Step j) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the isocyanate of formula (19)  ; or adding the product of Step j) above to ethyl chloroformate or isobutyl chloroformate, triethylamine, and tetrahydrofuran at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (19)  ;

l) adding the product of Step k) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (20)

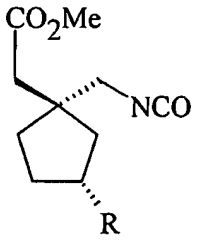
 ;

m) adding the product of Step l) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a compound of formula IIa  ;

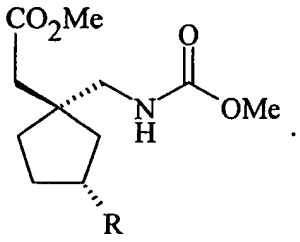
n) converting the product of Step m) to a compound of Formula II  , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

12. A process according to Claim 9, further characterized in that the intermediate product (14)  formed is further reacted, without isolation, with *tert*-butyl alcohol to produce the ester of formula (15) 

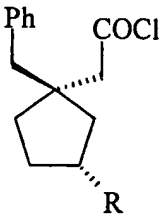
13. A process according to Claim 9, characterized in that the intermediate

product (19)  formed is further reacted, without isolation,

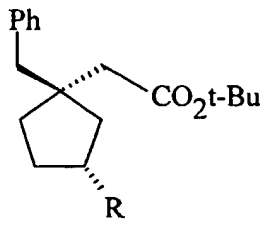
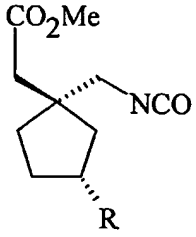
with methanol to produce the carbamate of formula (20)



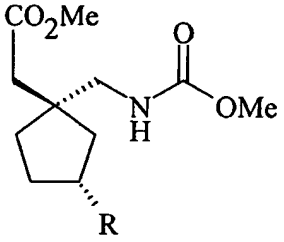
14. A process according to Claim 9, characterized in that the intermediate

product (14)  formed is further reacted, without isolation,

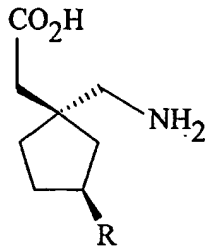
with *tert*-butyl alcohol to produce the ester of formula (15)

 , and the intermediate product (19) 

formed is further reacted, without isolation, with methanol to produce the

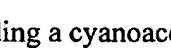
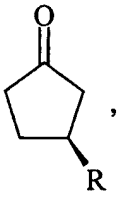
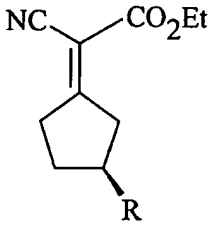
carbamate of formula (20)  .

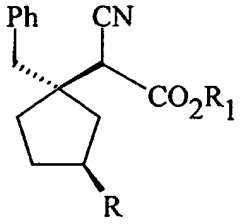
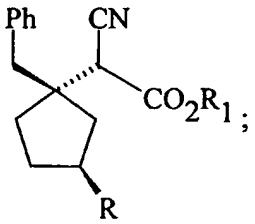
15. A process for the preparation of a compound of Formula III



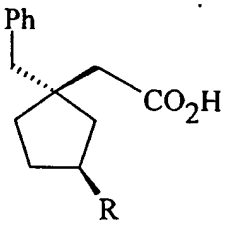
III

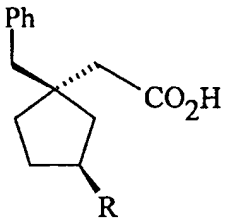
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)  , a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (22)  ;

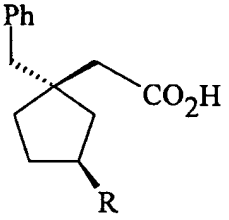
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition of products of formulas (23a)  and (23b)  ;

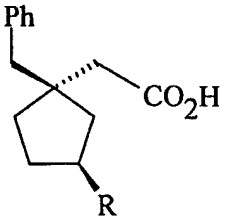
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying

to produce the carboxylic acids of formulas (24a) 

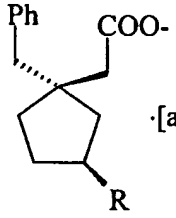
and (24b)  ; or

adding the products of Step b) above to an acid mixture, and stirring

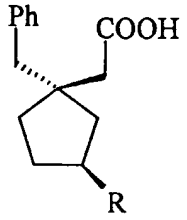
to produce the carboxylic acids of formulas (24a) 

and (24b)  ;

d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

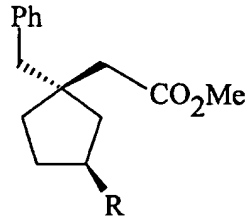
diastereomer of formula (25)  ·[amine-H]$^+$ as the amine salt; and

e) converting the product of Step d) to a carboxylic acid of formula (26)

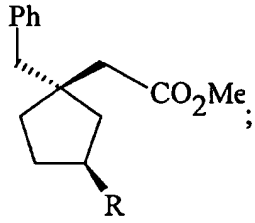


;

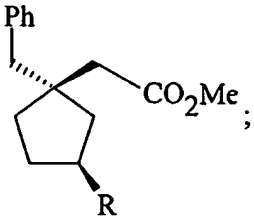
f) adding the product of Step e) to a mixture of iodomethane, a solvent, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and stirring to produce the ester of formula (27)



; or adding the product of Step e) to methanol and an acid to produce the ester of formula (27)

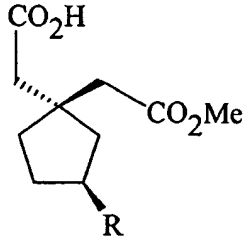


; or adding the product of Step e) to a solution of diazomethane or trimethylsilyl-diazomethane in a solvent to produce ester of formula (27)

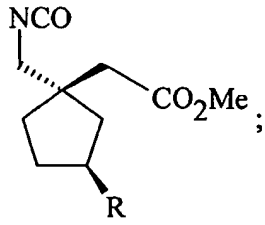


;

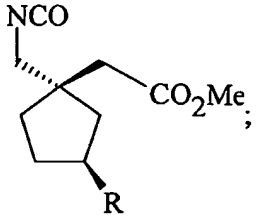
g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (28)



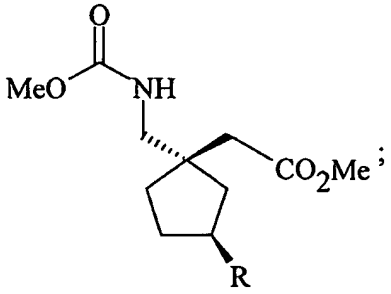
;

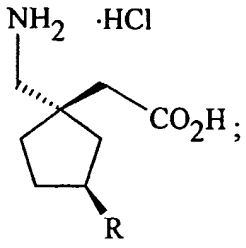
h) adding the product of Step g) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the isocyanate of formula (29)  ; or

adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (29)

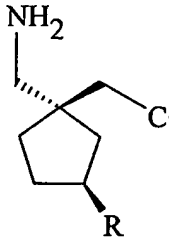


i) adding the product of Step h) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (30)



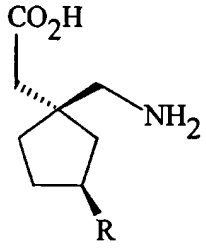
j) adding the product of Step i) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (IIIa)  ;

k) converting the product of Step j) to a compound of formula (III)



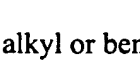
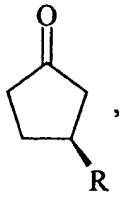
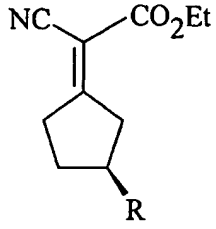
, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

16. A process for the preparation of a compound of Formula IV



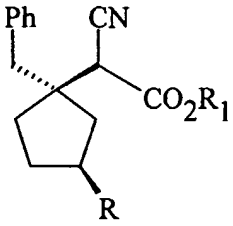
IV

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

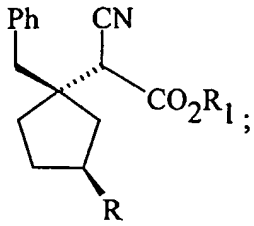
a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)  , a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (22)  ;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent

to produce the addition of products of formulas (23a)



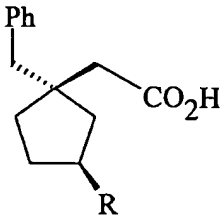
and (23b)



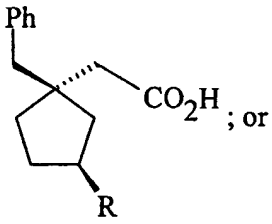
;

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying

to produce the carboxylic acids of formulas (24a)



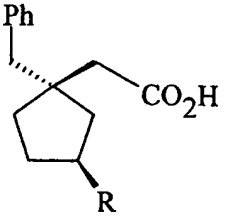
and (24b)



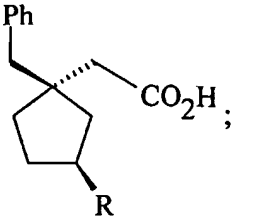
; or

adding the products of Step b) above to an acid mixture, and stirring

to produce the carboxylic acids of formulas (24a)

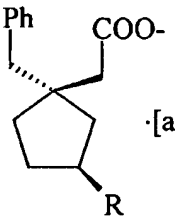


and (24b)

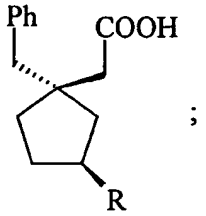


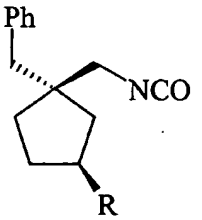
;

d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

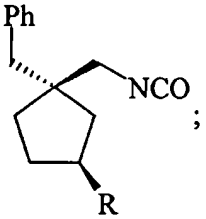
diastereomer of formula (25)  ·[amine-H]$^+$ as the amine salt; and

e) converting the product of Step d) to a carboxylic acid of formula (26)

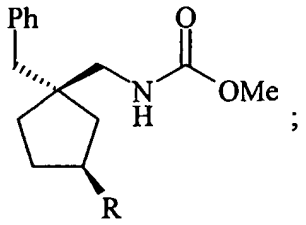
 ;

f) adding the product of Step e) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA) is added, and stirring to produce the isocyanate of formula (31)  ; or

adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate of formula (31)

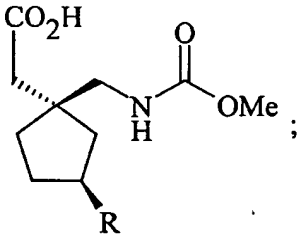
 ;

g) adding the product of Step f) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (32)



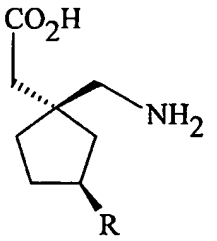
;

h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (33)



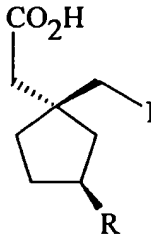
;

i) adding the product of Step h) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (IVa)



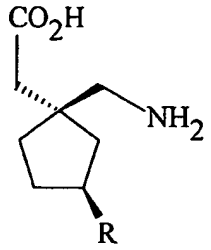
·HCl ; and

j) converting the product of Step i) to a compound of formula (IV)



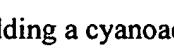
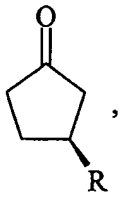
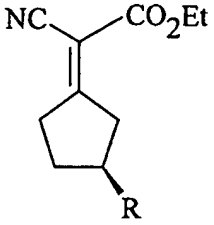
, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

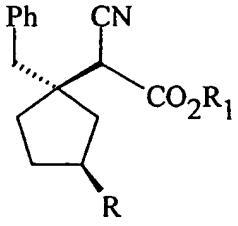
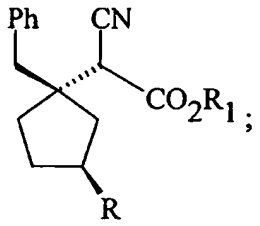
17. A process for the preparation of a compound of Formula IV



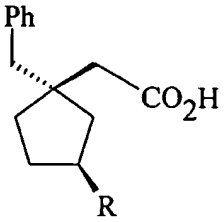
IV

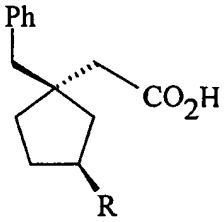
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)  , a solvent, a carboxylic acid, and a Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of formula (22)  ;

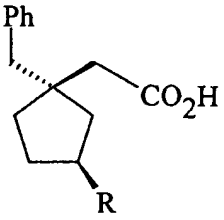
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition of products of formulas (23a)  and (23b)  ;

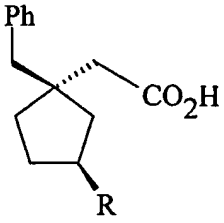
c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying

to produce the carboxylic acids of formulas (24a) 

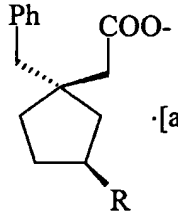
and (24b)  ; or

adding the products of Step b) above to an acid mixture, and stirring

to produce the carboxylic acids of formulas (24a) 

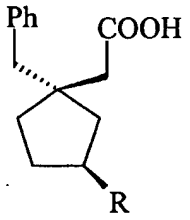
and (24b)  ;

d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

diastereomer of formula (25)  ·[amine-H]$^+$ as the amine

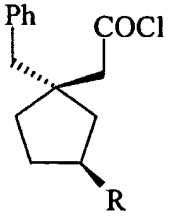
salt; and

e) converting the product of Step d) to a carboxylic acid of formula (26)



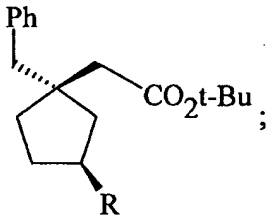
;

f) adding oxalyl chloride to a mixture of the product of Step e), a solvent, and N,N-dimethylformamide (DMF), and stirring to produce the acid chloride of formula (34)



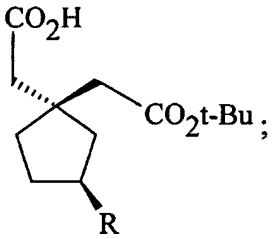
;

g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent, and a tertiary amine base, and stirring to produce the ester of formula (35)



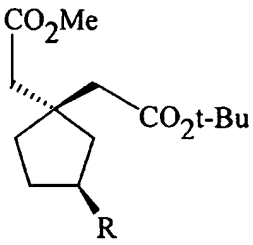
;

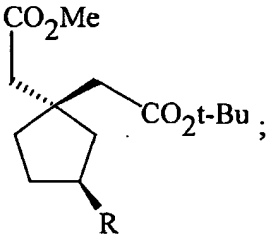
h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (36)



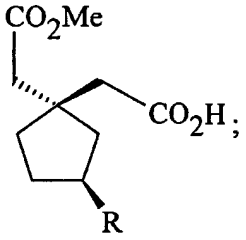
;

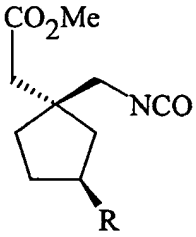
i) adding the product of Step h) to a mixture of a solvent, methanol, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of

formula (37)  ; or adding the product of Step h)

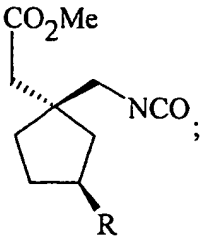
to a mixture of iodomethane, a solvent, and a base, and stirring to produce the bis ester of formula (37)  ;

j) adding an acid to a mixture of the product from Step i) and a solvent and stirring to produce the carboxylic acid of formula (38)

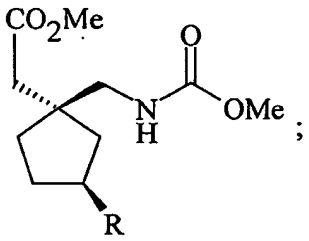


k) adding the product of Step j) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the isocyanate of formula (39)  ; or adding the product of Step j) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and

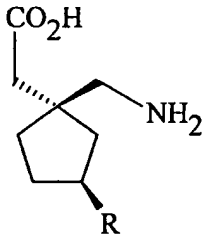
tetrahydrofuran or acetone, followed by adding toluene or benzene,

and refluxing to produce isocyanate of formula (39)  ;

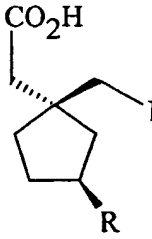
l) adding the product of Step k) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (40)

 ;

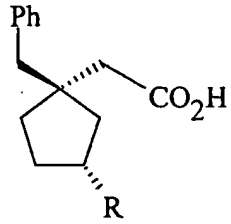
m) adding the product of Step l) to a mixture of a solvent and hydrochloric acid, and stirring to produce a compound of

formula (IVa)  ;

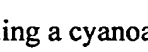
n) converting the product of Step m) to a compound of Formula IV

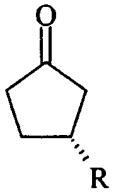
 , and further converting, if desired, to a pharmaceutically acceptable salt by known means.

18. A process for the preparation of a compound of formula (6)

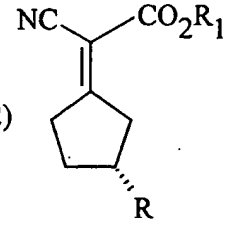

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and

pharmaceutically acceptable salts thereof, which comprises:

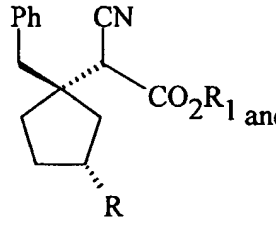
a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of

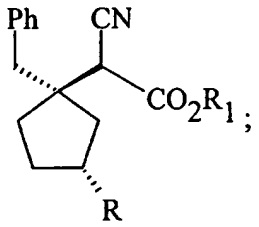
formula (1)  , a solvent, a carboxylic acid, and a

Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of

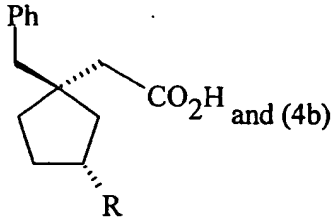
formula (2)  ;

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition

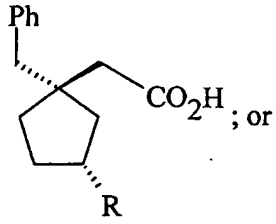
products of formulas (3a)  and (3b)

 ;

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, and a solvent, and stirring, and then acidifying to produce the carboxylic acids of formulas (4a)

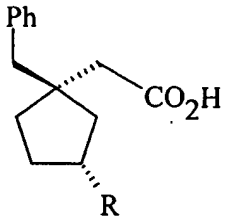


and (4b)

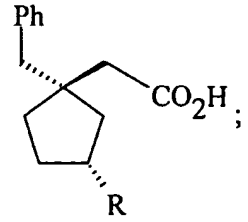


; or

adding the products of Step b) above to an acid mixture and stirring to produce the carboxylic acids of formulas (4a)

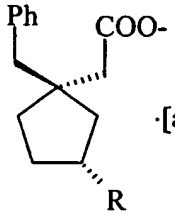


and (4b)



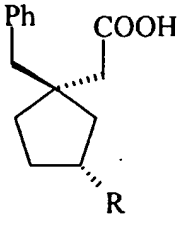
;

d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (5)

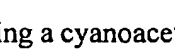
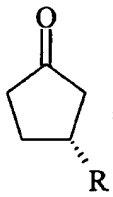


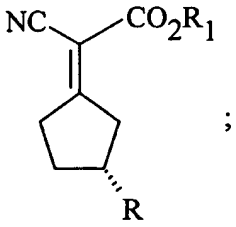
·[amine-H]$^+$ as the amine salt; and

e) converting the product of Step d) to a carboxylic acid of formula (6)

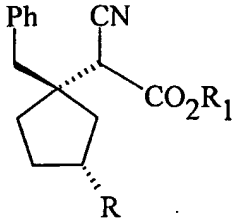
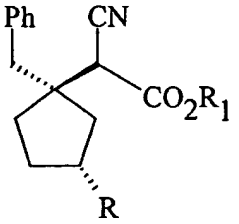


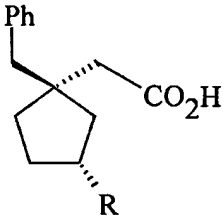
19. A process according to Claim 18 which comprises:

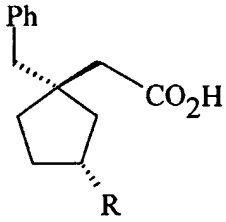
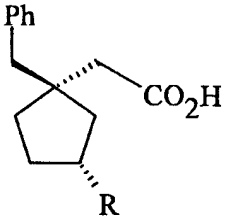
a) adding a cyanoacetate of formula (A)  wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of formula (1)  , a solvent selected from tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

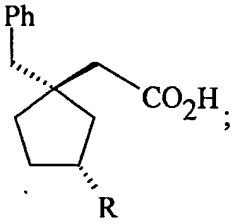
 ;

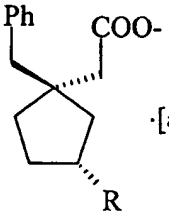
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and

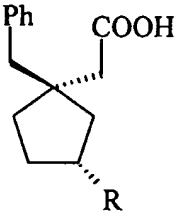
tert-butyl methyl ether to produce the addition products of formulas (3a)  and (3b)  ;

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture, and then acidifying to produce the carboxylic acids of formulas (4a)  and (4b)

 ; or adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H_2SO_4, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of formulas (4a) 

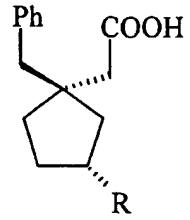
and (4b)  ;

d) contacting the products of Step c) above with an amine selected from (S)-α-methyl-benzylamine, (R)-α-methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$ as the amine salt; and

e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid dissolved in acetic acid and water, and stirring to produce the carboxylic acid of formula (6)  ; or

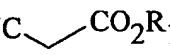
partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and

evaporating the organic layer to produce the carboxylic acid of

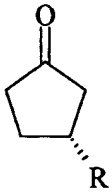
formula (6) 

.

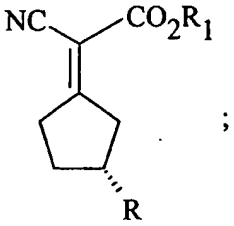
20. A process according to Claim 18 which comprises:

a) adding a cyanoacetate of formula (A) 

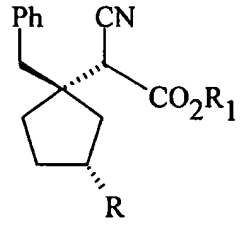
, wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)

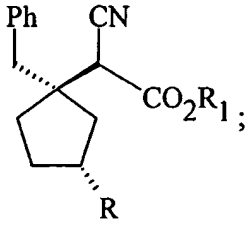


, toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)

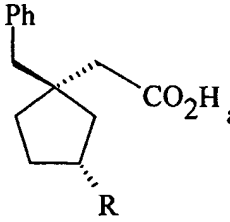
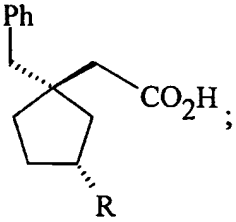


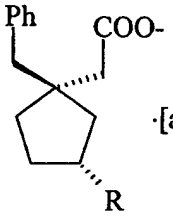
;

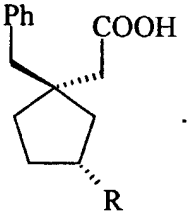
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition products of formulas (3a) 

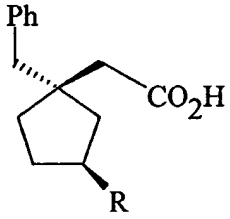
and (3b) 

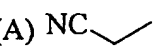
;

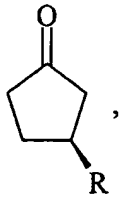
c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of formulas (4a)  and (4b)  ;

d) contacting the products of Step c) above with (S)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (5)  ·[amine-H]$^+$ as the (S)-α-methyl-benzylamine salt;

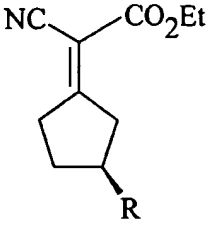
e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (6) 

21. A process for the preparation of a compound of formula (26)  wherein R is C_1-C_{10} alkyl or C_1-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

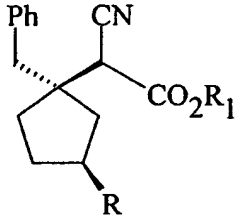
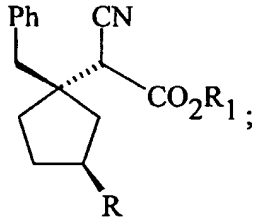
a) adding a cyanoacetate of formula (A)  , wherein R_1 is alkyl or benzyl, to a mixture of a chiral cyclopentanone of

formula (21)  , a solvent, a carboxylic acid, and a

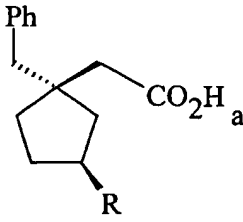
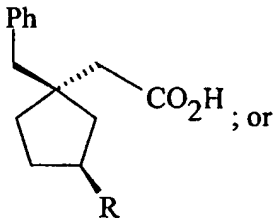
Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of

formula (22)  ;

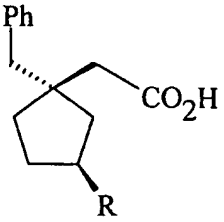
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition of products of formulas (23a)

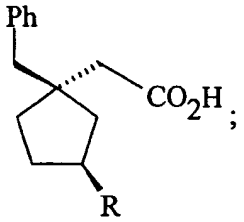
 and (23b)  ;

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, and a solvent, and stirring, and then acidifying to produce the carboxylic acids of formulas (24a)

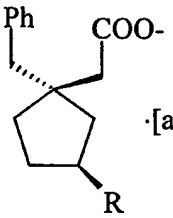
 and (24b)  ; or

adding the products of Step b) above to an acid mixture, and stirring

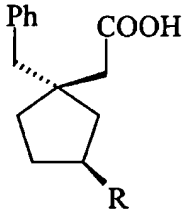
to produce the carboxylic acids of formulas (24a) 

and (24b)  ;

d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

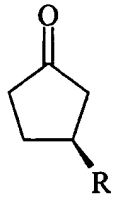
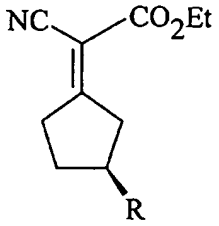
diastereomer of formula (25)  ·[amine-H]$^+$ as the amine salt; and

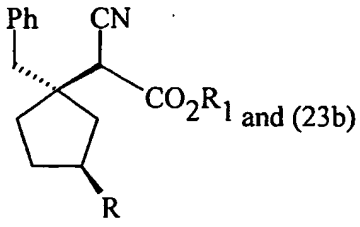
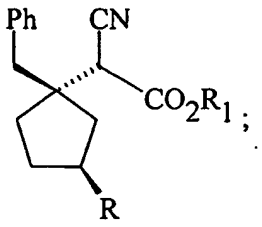
e) converting the product of Step d) to a carboxylic acid of formula (26)



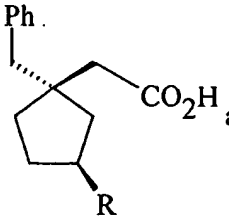
22. A process according to Claim 21 which comprises:

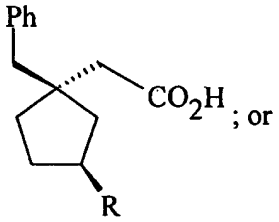
a) adding a cyanoacetate of formula (A)  , wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl, to a mixture of a chiral

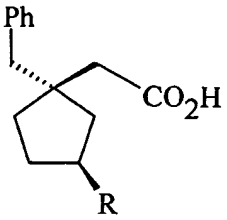
cyclopentanone of formula (21)  , a solvent selected from tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (22)  ;

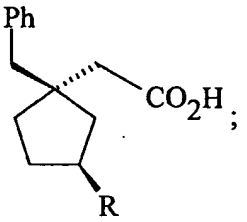
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce the addition products of formulas (23a)  and (23b)  ;

c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and

stirring the mixture, and then acidifying to produce the carboxylic acids of formulas (24a)  and (24b)

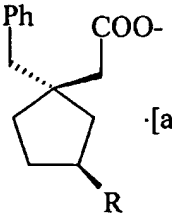
 ; or

adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H_2SO_4, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of formulas (24a)  and (24b)

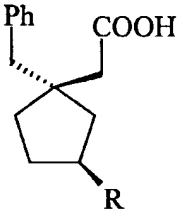
 ;

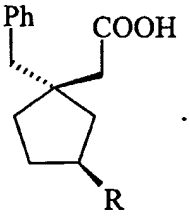
d) contacting the products of Step c) above with an amine selected from (S)-α-methyl-benzylamine, (R)-α-methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile,

tert-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the enriched

diastereomer of formula (25)  ·[amine-H]$^+$ as the amine salt; and

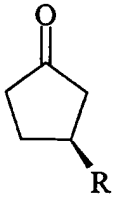
e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid dissolved in acetic acid and water, and stirring to produce the

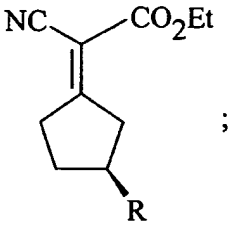
carboxylic acid of formula (26)  ; or

partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of formula (26)  .

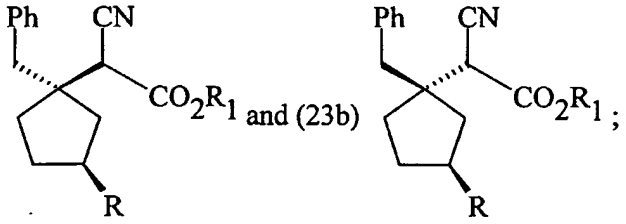
23. A process according to Claim 21 which comprises:

a) adding a cyanoacetate of formula (A) , wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (21)


, toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (22)

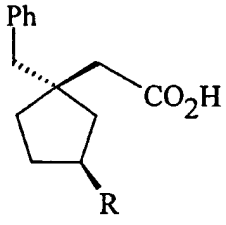

;

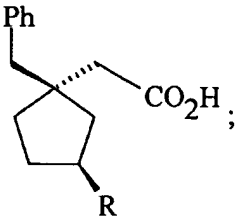
b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to -20°C to produce the addition products of formulas (23a)


and (23b)

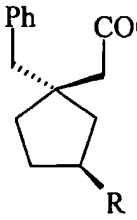
;

c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of formulas (24a)

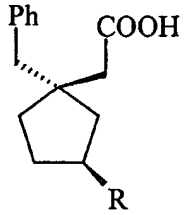

and (24b)

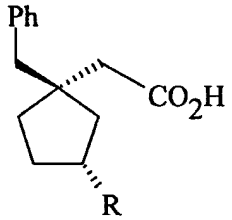

;

d) contacting the products of Step c) above with (R)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of

formula (25)  ·[amine-H]$^+$ as the (R)-α-methyl-benzylamine salt; and

e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (26)

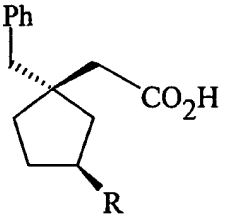


24. A compound of formula (6)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof.

25. A compound according to Claim 24 wherein R is C_1-C_{10} alkyl.

26. A compound according to Claim 24 wherein R is selected from methyl, ethyl, and *n*-propyl.

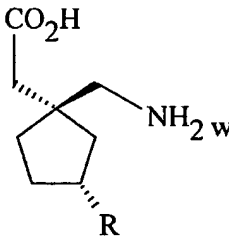
27. A compound according to Claim 24 named ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid.

28. A compound of formula (26)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof.

29. A compound according to Claim 28 wherein R is C_1-C_{10} alkyl.

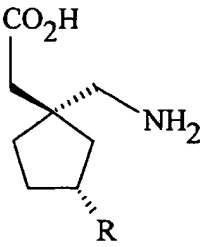
30. A compound according to Claim 28 wherein R is selected from methyl, ethyl, and *n*-propyl.

31. A compound according to Claim 28 named ((1R,3S)-1-benzyl-3-methyl-cyclopentyl)-acetic acid.

32. A compound of Formula I  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 1.

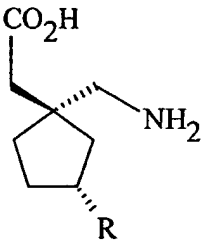
33. A compound according to Claim 32 wherein R is selected from methyl, ethyl, and *n*-propyl.

34. A compound according to Claim 32 selected from ((1R,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid and ((1R,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride.

35. A compound of Formula II  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 5.

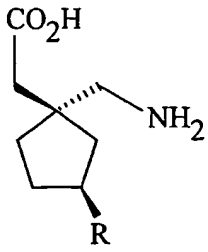
36. A compound according to Claim 35 wherein R is selected from methyl, ethyl, and *n*-propyl.

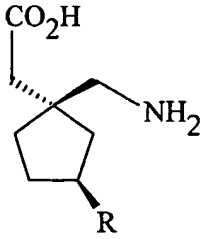
37. A compound according to Claim 35 selected from ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid and ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride.

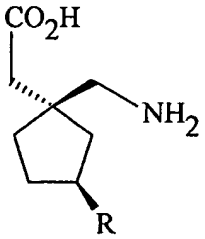
38. A compound of Formula II  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 9.

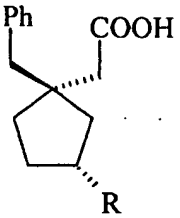
39. A compound according to Claim 38 wherein R is selected from methyl, ethyl, and *n*-propyl.

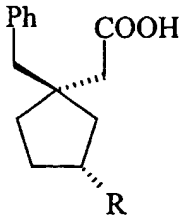
40. A compound according to Claim 38 selected from ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid and ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride.

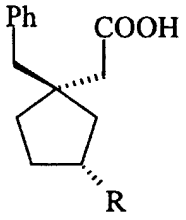
41. A compound of Formula III  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 15.

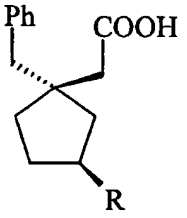
42. A compound of Formula IV  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 16.

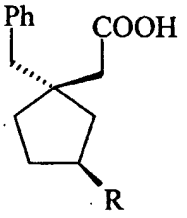
43. A compound of Formula IV  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 17.

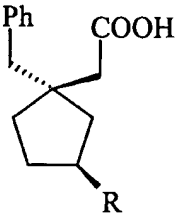
44. A compound of formula (6)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 18.

45. A compound of formula (6)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 19.

46. A compound of formula (6)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 20.

47. A compound of formula (26)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 21.

48. A compound of formula (26)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 22.

49. A compound of formula (26) 

wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 23.

50. A compound selected from:

E-Cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester;

Z-Cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester;

(R)-((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester;

(S)-((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester;

(R)-((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester;

(S)-((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester;

((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentylmethyl)-benzene;

((1S,3R)-1-Benzyl-3-methyl-cyclopentylmethyl)-carbamic acid methyl ester;

[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid;

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid methyl ester;

(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid;

((1R,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester;

[(1R,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester;

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid *tert*-butyl ester;

[(1S,3R)-1-Carboxymethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester;

[(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester;

((1R,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid;

((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester; and

[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester.

51. A compound selected from:

((1R,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

((1R,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

((1R,3R)-1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

((1R,3R)-1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid hydrochloride;

((1R,3R)-1-Aminomethyl-3-propyl-cyclopentyl)-acetic acid; and

((1R,3R)-1-Aminomethyl-3-propyl-cyclopentyl)-acetic acid hydrochloride.

52. A compound selected from:

((1S,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

((1S,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

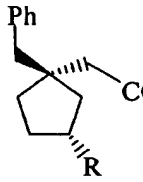
((1S,3R)-1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

((1S,3R)-1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid hydrochloride;

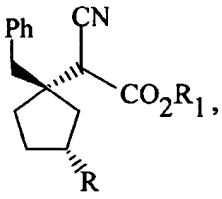
((1S,3R)-1-Aminomethyl-3-propyl-cyclopentyl)-acetic acid; and

((1S,3R)-1-Aminomethyl-3-propyl-cyclopentyl)-acetic acid hydrochloride.

53. A process for the preparation of a compound of formula (4a)

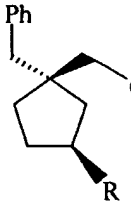


wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl,

comprising, hydrolyzing a compound of formula (3a)  ,

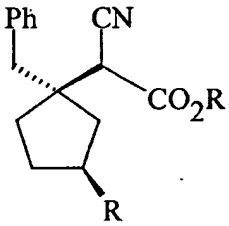
wherein R_1 is H, alkyl, or benzyl.

54. A process for the preparation of a compound of formula (24a)



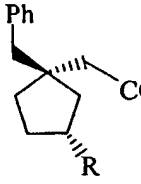
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl,

comprising, hydrolyzing a compound of formula (23a)



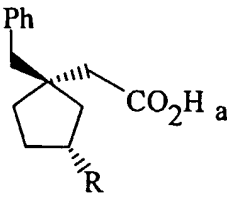
, wherein R_1 is H, alkyl, or benzyl.

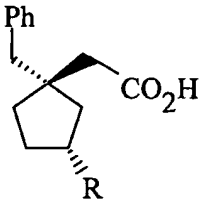
55. A process for the preparation of a compound of formula (6)



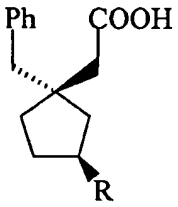
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl,

comprising, resolving a

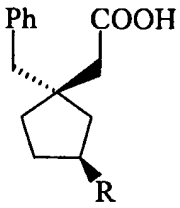
mixture containing compounds of formulas (4a)  and

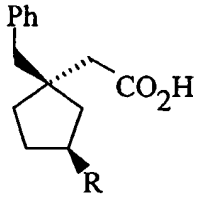
(4b)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl.

56. A process for the preparation of a compound of formula (26)

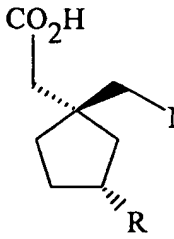
 wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl,

comprising, resolving a

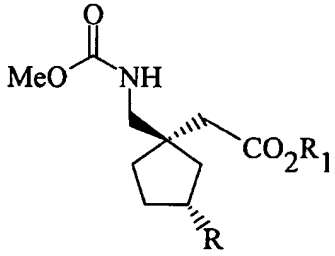
mixture containing compounds of formulas (24a)  and

(24b)  wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl.

57. A process for the preparation of a compound of Formula I

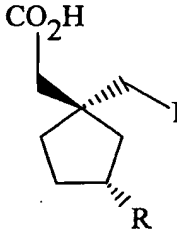


wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and a pharmaceutically acceptable salts thereof, comprising, hydrolyzing a compound of formula (41)

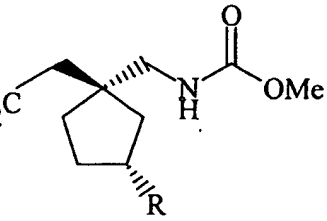


, wherein R_1 is H, alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

58. A process for the preparation of a compound of Formula II

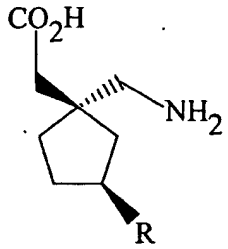


wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and a pharmaceutically acceptable salts thereof, comprising, hydrolyzing a compound of formula (42)



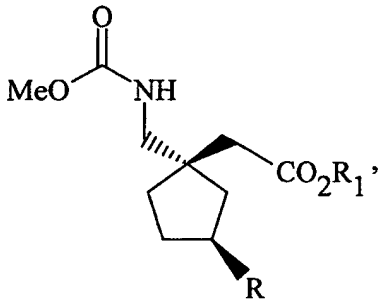
, wherein R_1 is H, alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

59. A process for the preparation of a compound of Formula III



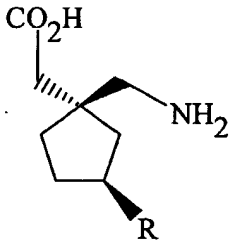
wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and

pharmaceutically acceptable salts thereof, comprising, hydrolyzing a

compound of formula (43)  , wherein R_1 is

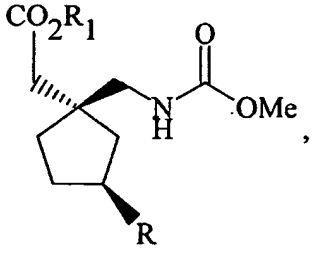
H, alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

60. A process for the preparation of a compound of Formula IV



wherein R is C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl, and

pharmaceutically acceptable salts thereof, comprising, hydrolyzing a

compound of formula (44)  , wherein R_1 is H,

alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

INTERNATIONAL SEARCH REPORT

Intern I Application No
PCT/US 00/32570

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C227/32 C07C229/28 C07C57/46 C07C255/31 C07C255/41
C07C265/08 C07C271/12 C07C69/616

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WERNER HERZ: "Azulenes. VII. A Novel Rearrangement in the Synthesis of Azulenes" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 78, no. 7, 5 April 1956 (1956-04-05), pages 1485-1494, XP002161288 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 1493, column 2, line 57 -page 1494, column 1, line 26 --- -/--	1,5,9, 15-18, 21,50

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 February 2001	16/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

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INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT/US 00/32570

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 21824 A (WARNER-LAMBERT) 6 May 1999 (1999-05-06) page 4, line 12 - line 21; page 6, line 1 - line 10; table 1; examples 3,9	32-43, 51,52
A	claims	1,5,9, 15-18, 21,24, 28, 44-50, 53-60

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/US 00/32570

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921824 A	06-05-1999	AU 9663898 A	17-05-1999
		BR 9813284 A	22-08-2000
		CN 1276784 T	13-12-2000
		EP 1032555 A	06-09-2000
		NO 20002118 A	26-04-2000
		ZA 9809740 A	25-04-1999